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NORTH AMERICAN BLASTOMYCOSIS

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North American blastomycosis is primarily a pulmonary disease caused by *Blastomyces dermatitidis*, a fungus which was first described by T. C. Gilchrist in 1896[48]. It is the purpose of this paper to discuss the pathogenesis, clinical picture and treatment of North American blastomycosis in light of the recent literature and our own experience.

GEOGRAPHICAL DISTRIBUTION. The disease is almost restricted to the North American continent. A recent epidemiological survey (Chasen[17]) showed that Wisconsin, Illinois, Ohio, Kentucky, North Carolina, and Tennessee are the states where clinical cases are most frequently seen. It was concluded that the true incidence is higher in the aforementioned areas since in such medically well supervised areas as New York and New England hardly any cases of blastomycosis are seen. Outside the United States, Canada has a moderate number (Elliot, Wilt and Duggan[34], Gaumond[47], Grandbois *et al.*[50], Poirier[102], Watson, Moore and Blank[141]) of cases and isolated instances have been reported from Mexico (Brody[11], Martinez, Reyes and Gonzales Ochoa[83]) and Venezuela (Montemayer[92]). Brody[11] observed a patient in Great Britain who almost certainly was infected in the United States. The European literature frequently groups under the heading of "blastomycosis" diseases caused by various yeast-like organisms (Borelli[10]) (*Cryptococcus neoformans*, Candida, *Blastomyces dermatitidis*) and most cases outside the North American continent are poorly documented (Chasen[17], Foldvari and Florian[41], Joulia and Le Coulant[63], Kovacs[67], Muller and Hilscher[95], Schoenmackers[115], Wegman[144]).

The reason why the disease is essentially restricted to the North American continent, and, within the continent, to the above mentioned areas is not clear. The same puzzling epidemiology can be found in histoplasmosis which

is so prevalent in the Mississippi Valley, and in coccidioidomycosis which occurs mostly in Southwestern United States. Other infectious diseases have geographic restrictions; for instance, Oroya fever which, even within Peru, is restricted to a small area.

EPIDEMIOLOGY. The organism has not been isolated from sources in nature in spite of numerous attempts, including our own. Emmons has demonstrated[35] that *B. dermatitidis* can grow in artificially infected garden soil and Menges has grown it on tree bark[90]. Although no proof exists that soil is the source of infection, it certainly is suggestive, especially if one considers the isolation from soil of fungi which show similar epidemiologic patterns (*H. capsulatum, C. immitis*) (Emmons[35]). The only *bona fide* epidemic was observed in North Carolina (Smith *et al.*[127]). Another was supposed to have occurred in service men in Okinawa but no facts are available to substantiate the claim. Extensive inquiries by the Army and personal contact with the head of the laboratory in Manila failed completely to substantiate the claim for the presence of the reported epidemic (Schwarz and Baum[119]).

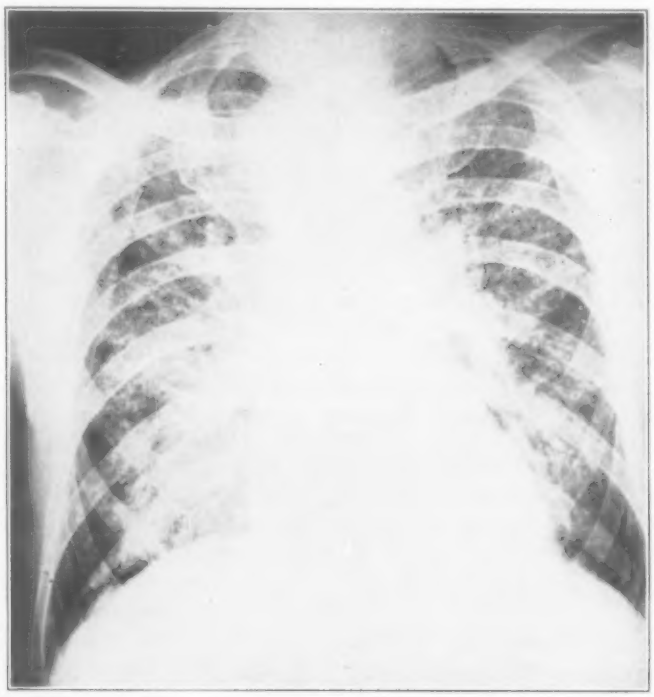

Fig. 1.—The roentgenographic pictures can vary from nonspecific infiltrates to cavitary lesions. White male (84 years) with widespread pulmonary disease. Organisms recovered from sputum.

PATHOGENESIS. The disease blastomycosis has long been considered to be cutaneous in origin with either secondary or "rare" primary pulmonary involvement. The present authors have repeatedly pointed out that blastomycosis originates in the lung and only

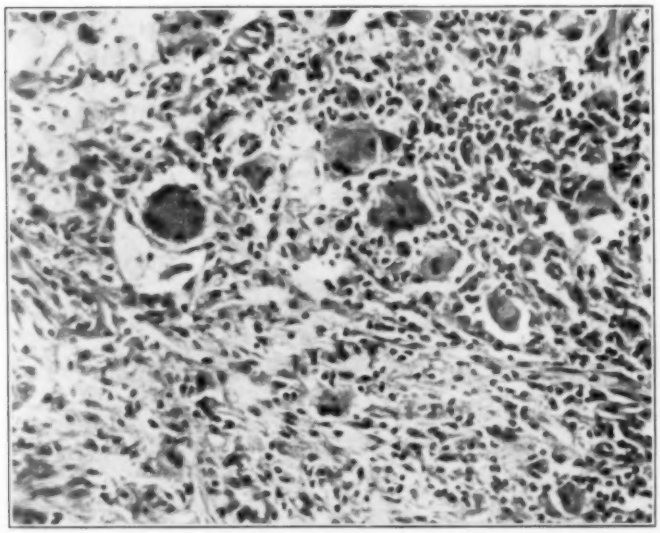

Fig. 2.—The pulmonary lesions are frequently proliferative with numerous giant cells which often contain the causative organisms. 340× H.E.

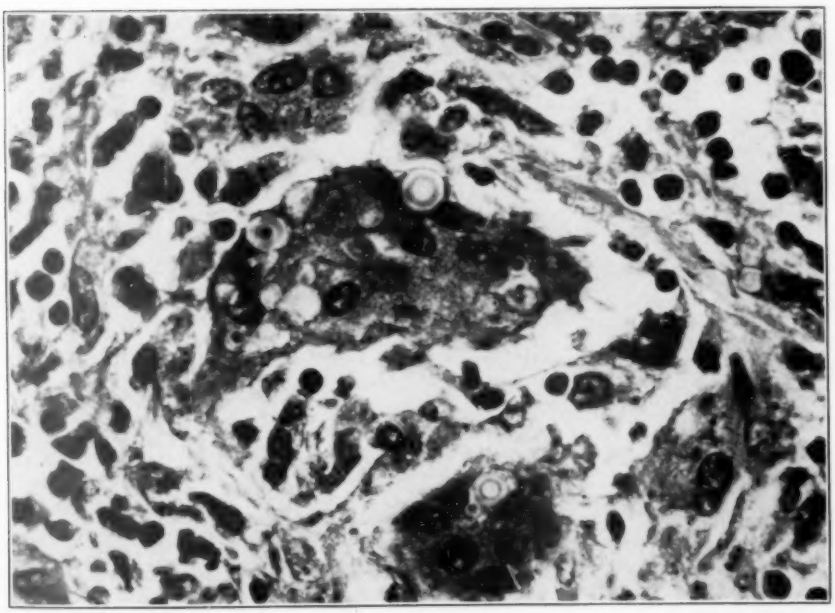

Fig. 3.—Multinucleated giant cell with prominent thick walled organisms. Other blastomycetes are seen in extracellular granulation tissue. H.E. 1200×.

then spreads to the skin and other organs (Schwarz and Baum[116,118,120]). The granulomatous diseases produce a primary lesion or chancre on the point of entrance of the causative organism from which the regional lymph nodes become involved with regularity. This primary complex can be found anatomically in almost every case of blastomycosis, if searched for.

The pulmonary origin of blastomycosis has to be postulated on positive and negative facts (Schwarz and Baum[116,118]). In the former group belongs the great frequency with which pulmonary blastomycosis can be demonstrated clinically and radiologically. Even more impressive is the almost constant necropsy finding of pulmonary lesions. The pulmonary lesion may become arrested even in the presence of active extrapulmonary pathology (cutaneous, prostatic, and others). Occasionally at necropsy prolonged search may be necessary to demonstrate the pulmonary lesion. Furthermore, pulmonary blastomycosis frequently is found without skin manifestations. It may be difficult to demonstrate lung lesions clinically but skin lesions are easily diagnosed. The epidemic reported from North Carolina is a beautiful ex-

Fig. 4.—Several layers of recurrent pleuritic inflammation topped by fibrinous exudate are often found covering blastomycotic pneumonitis. 140× H.E.

ample of respiratory infection in a group of persons living in a rather small geographic area (Smith *et al.*[127]).

Lymphadenitis secondary to skin lesions is absent unless we are dealing with one of the exceptional cases of primary (inoculation) blastomycosis of the skin which will be discussed later (Schwarz and Baum[116], Wilson *et al.*[148]). Once we have accepted the lung as portal of entrance, it is not difficult to understand why, even in the presence of progressive skin lesions, pulmonary involvement may clinically not be demonstrable. Pulmonary blastomycosis can fortunately become arrested spontaneously or after treatment and we have seen proof of such healing repeatedly. It is the case with an arrested pulmonary lesion where surgical removal of an isolated skin lesion will produce rapid and often permanent "cure."

In dogs a considerable experience has accumulated about spontaneous blastomycosis and the picture is identical with the human situation: constant pulmonary involvement, sometimes with cutaneous metastasis. Primary pulmonary complexes have been demonstrated (Newberne, Neal and Heath[98], Robbins[108], Robinson and Schell[109]).

Differences exist in the morphologic picture between true inoculation (primary) cutaneous blastomycosis and the commonly seen (secondary) skin involvement.

One of the negative facts, in the argument of the pulmonary origin of the disease, is absence of a local "primary complex" in all skin (secondary) cases, except in true cutaneous inoculation, which so far has occurred only in laboratory workers (Schwarz and Baum[116], Wilson *et al.*[148]). Another negative fact is the history of "trauma" which is worthless in most cases. Trauma can be accepted only if *Blastomyces dermatitidis* can be demonstrated on the traumatizing agent. This was the case in the laboratory infections which have been mentioned before. *Blastomyces dermatitidis* has not been demonstrated in nature, even if it is reasonably probable that it must exist in soil. The unreliability of the history of trauma is well illustrated by the following case report (Schwarz and Baum[116]).

> A foundry worker burned his left wrist in molten iron. Obviously the temperature of the liquid metal precluded entirely the presence of living microorganisms. Several weeks later the patient presented himself with symmetrical blastomycosis of both wrists. The cutaneous manifestations are understandable only if they are interpreted as seeding from the lung in a *locus minoris resistentiae*, here produced by a burn.

The few true primary skin infections have been inoculations in the laboratory and are quite thoroughly discussed by Wilson *et al.*[148]. Small cuts incurred during necropsies or puncture wounds produced with needles during culture work were the means of infection. Invariably a local sore developed followed either by lymphangitis or lymphadenitis, or both. All reported cases become arrested after reaching the axillary lymph nodes. In one case the axillary lymph nodes were excised because of suspicion of Hodgkin's disease and *Blastomyces dermatitidis* was found in the lymph nodes. The anatomical picture is quite different from the "common" case with secondary skin involvement. In the latter lymphangitis and lymphadenitis are missing and as far as the morphology of the skin lesions goes, Wilson *et al.* believe[148] that even within the great variability of the clinical cutaneous involvement a different character can be recognized.

We have followed a case of pulmonary blastomycosis in whom repeated cutaneous embolization was observed.

Deep seated infiltrates were palpated long before they could be seen. Slowly within several days the skin turned red, fluctuation became apparent, and finally the surface ulcerated and drained small amounts of exudate. Another case very much in point and illustrating the hematogenous spread and the origin of skin lesions has been previously described (Schwarz and Baum[116]). The patient developed an acute arthritis of the right ankle without a break of the skin. Roentgenograms taken shortly after the onset showed a miliary pulmonary disease considered at this time to be tuberculosis. A few weeks later the patient developed a "typical blastomycosis" of the skin and died subsequently of widespread blastomycosis. Had no roentgenograms been taken at the time of the arthritis an inverse sequence could have been constructed.

While many experienced authors have become convinced of the pulmonary nature of the disease, persons who only occasionally come in contact with blastomycosis are still impressed by the presence of obvious skin lesions and the associated history of trauma. It may be well to remember that many breast tumors including carcinoma are seen in which the patient describes a related single trauma to the breast, yet most observers reject any true etiologic relationship. We feel the same way about the relationship of trauma to the onset of blastomycosis, particularly since no one has demonstrated *Blastomyces dermatitidis* on normal skin or in nature. Lately Macauley[79] has discussed in a dispassionate way the pros and cons of the possibility of primary cutaneous infection.

EPIDEMICS OF BLASTOMYCOSIS. Only one epidemic of blastomycosis has so far been reported in contrast with the rather common focal outbreaks of histoplasmosis. The former occurred in a small community in North Carolina (Harris *et al.*[56], Smith *et al.*[127]) where within a few months 11 cases of blastomycosis were recognized. The disease was also seen in children, which is rather uncommon in blastomycosis; the youngest was only 7 weeks old at the time of death. Subsequent skin testing in the community has been carried out. Of approximately 1400 people tested 88 reacted positively to histoplasmin, and 42 positively to Blastomyces vaccine. Eleven of the 88 who reacted to histoplasmin simultaneously had Blastomyces-vaccine reaction. The tests were not done in the best of conditions since three different lots of histoplasmin were used at different times. The possibility of some of the "positive" blastomycin reactors being cross reactors to histoplasmin cannot completely be ruled out. None of the reactors had roentgenographic or clinical evidence of disease. Several of the persons who had positive titers of complement fixing antibodies for *B. dermatitidis* had negative skin reactions to Blastomyces vaccine. The authors express the opinion that blastomycosis and histoplasmosis may have a similar mechanism of infection and the dual reactions may not represent "cross-reactions" but true double infection. All efforts to trace the infection to soil, water or direct contact were unsuccessful.

An occurrence of 4 cases in Bolivar County (Mississippi) is mentioned by Chick *et al.*[19]. No common source was established in the 4 cases.

BLASTOMYCOSIS ABROAD. Reports from abroad especially from Europe have appeared and the possibility that *B. dermatitidis* has been overlooked or misinterpreted cannot be ruled out. Completely uncritical reports like the ones of Foldvari[40,41] where patients are classified as "European" or "North American" blastomycosis without giving any cultural or morphologic infor-

mation do not contribute to objective knowledge.

A case from Venezuela (Montemayer[92], Polo, Brass and Montemayer[103]) and one from Mexico (Martinez, Reyes and Gonzales Ochoa[83]) are *bona fide* cases verified by morphologic and cultural procedures. The Mexican case had worked for 8 months in California 4 years prior to his clinical disease. Reports from India (Jayaram *et al.*[62]), France (Monod and Mahassen[91]), Australia (O'Donaghue[99]), Spain (Garcia and Ledesma[46]), and Hungary (Foldvari and Florian[40,41], Lövei and Bogsch[77], Muray[96], Snekszer[129]), are to our mind unacceptable because the identifying information is either absent, or incomplete. Other reports, such as a recent French paper (Monod and Mahassen[91]) speak at length of North American blastomycosis, only to note finally the resection of a pulmonary lesion, from which *Candida tropicalis* was cultured. Therefore, it is safe to state that the disease caused by *Blastomyces dermatitidis* almost without exception is found on the North American continent. Vermeil *et al.*[139] report an authentic case from Tunis in a 25-year-old man whose geographical history was not given. He died of generalized blastomycosis. (According to Drouhet[28] an "atypical" strain of *Blastomyces dermatitidis* was cultured.) Assuming that the man was never on the North American continent, this would constitute one of the rare cases occurring abroad. Skin testing done in the Belgian Congo has been reported as essentially negative (Leduc[72], Lucasse, Duquenoy and Otten[78]). An Australian case diagnosed from a biopsy is not well documented (McMillan[87]). A Swiss case was "diagnosed" on the basis of a positive skin reaction, and a C.F.T. of 1:16. There was no demonstration of organisms in this patient (Helmig[59]).

CLINICAL ASPECTS OF BLASTOMYCOSIS. In almost all cases blastomycosis is a primary pulmonary disease (Schwarz and Baum[116,118]). Dissemination of organisms from the primary lung focus to extrapulmonary locations, especially the skin leads to the common clinical picture of blastomycosis. The exceptional occurrence of primary skin lesions has been reported (Schwarz and Baum[116], Wilson *et al.*[148]) but in each instance the presence of lymphangitis and axillary lymphadenitis was observed. In addition very special circumstances led to the accidental inoculation of all of these cases. The pathogenesis is emphasized to aid in fuller understanding of the various clinical manifestations.

Clinically pulmonary blastomycosis is less commonly recognized than is the cutaneous syndrome. However, the presence of a pulmonary lesion (or lesions) in every case has been documented if it is looked for. Even though clinical or roentgenographic evidence of pulmonary involvement may be lacking careful anatomical studies reveal specific small pulmonary lesions or scars which substantiate the above statement (Schwarz and Baum[116]).

Acute primary pulmonary blastomycosis has been observed clinically in several instances (Baker, Warrick and Noojin[4], Smith *et al.*[127], Watson, Moore and Blank[141]). The North Carolina "epidemic" was well documented and the acute nature of the pulmonary process was quite evident (Harris *et al.*[56], Smith *et al.*[127]). These patients had pneumonic infiltrates demonstrated on chest roentgenogram and were acutely ill. All but a 7-month-old infant recovered with a positive blastomycin skin test as the only residual. Very little, if any pulmonary sequelae were noted. Except for the positive cultures there was nothing to differentiate this

syndrome from any other acute bronchopneumonia.

The inference from this experience is that there may well be many such cases that are never recognized and who may never demonstrate "typical" clinical manifestations. Unfortunately there is no good diagnostic tool to test this hypothesis since the skin test is not consistently positive in blastomycosis. However, when the above mentioned anatomical data are correlated with this clinical experience the conclusion that subclinical pulmonary blastomycosis exists appears warranted.

The facts of pathogenesis of chronic pulmonary blastomycosis are not known. The original focus becoming arrested and then later breaking down, (endogenous reinfection) would be expected to be the usual course of events. It is unlikely that the same person after many years of "arrest" should become again the victim of *Blastomyces dermatitidis* from without.

The patients usually become debilitated chronically with weight loss, and have such nonspecific symptoms as: weakness, cough, sputum, hemoptysis, chest pain, fever, night sweats, and exertional dyspnea. Occasionally an acute fulminating course is seen which may be in association with generalized infection (Marx and Berenbaum[84]) or may be due to exclusive lung involvement (Baker, Warrick and Noojin[4], Steen, Foxworthy and Baker[130]).

The roentgenogram may reveal almost any type of pulmonary involvement. Pneumonic infiltrates, disseminated nodular infiltrates, strandlike densities with and without pleural thickening, hilar adenopathy, miliary densities and cavities have been observed (Felson and Heublein[37], Hawley and Felson[57]). Despite the nonspecific nature of all the described findings we wish to emphasize the cavitary type because of its possibility of confusion or combination (Black and Wilson[7], Layton, McKee and Stamler[71], Stillians and Klemptner[131]) with histoplasmosis, tuberculosis, coccidioidomycosis, actinomycosis and nocardiosis. Clinical descriptions of this type of blastomycosis have appeared but the lack of specificity is obvious (Acree, De Camp and Ochsner[2], Black and Wilson[7], Harrell, Bocobo and Curtis[54], Takero, Hopkins and Murphy[133], Weisel and Landis[146], White and Owen[147]).

Weisel and Landis examined cases of pulmonary blastomycosis bronchoscopically and felt that small endobronchial ulcers associated with glary red mucoid secretions were fairly specific[146].

One other suggestive if not actually diagnostic characteristic has been the presence of pleural disease of rather extensive nature without major accumulation of fluid. In one series of over 50 cases frequent "frosting" like lesions of the pleura were noted grossly but no pleural fluid was seen (Schwarz and Baum[116]). One report of pleural fluid which yielded *Blastomyces dermatitidis* on culture has been noted (Abraham and Luddecke[1]) and we have observed one case in which a similar situation was noted. However, major blastomycotic pleural effusion must be extremely rare.

One characteristic case was observed by us in which there was localized pleural pain for several weeks with an observed pulmonary lesion adjacent to the area of discomfort but at no time did demonstrable pleural fluid develop.

E.M.: This 43-year-old white woman was admitted to the hospital with a 4-week history of intermittant lower right anterior chest pain associated with a wheeze in this same area. She developed two subcutaneous nodules, cough and weakness up to the time of her admission to the hospital. Examination revealed an evanescent friction rub over the lower right anterior chest. Roentgenogram revealed right middle lobe infiltrate. Skin tests

for tuberculosis, histoplasmosis and blastomycosis were negative as were several sputum cultures for acid-fast bacilli. Despite this she was started on anti-tuberculous chemotherapy. She was discharged from the hospital but was readmitted in 12 days with the history of having developed numerous subcutaneous nodules. She was critically ill. Cultures of pus aspirated from the nodules and of sputum were positive for *Blastomyces dermatitidis*. A complement fixation test for blastomycosis was negative. Stilbamidine was then given for 43 days with good results but two of the skin lesions got worse subsequently and she received a second course of stilbamidine for 19 days in the hospital and an indeterminate period as an outpatient. All symptoms cleared and the patient has remained entirely well for 5 years.

To reemphasize the main point, blastomycosis of the lungs is the primary form of the disease and all other manifestations stem from the pulmonary lesions. The picture of pulmonary blastomycosis is clinically nonspecific except for the rarity of pleural fluid in the face of chronic pleurisy. Of importance is the association of prognosis and the state of the pulmonary lesions. Whether there has been cutaneous metastasis or not, if the pulmonary lesions become arrested the disease usually runs a benign course. In such an instance local treatment of lesions is usually met with success and no further metastatic foci occur. If, however, the pulmonary lesions are active, either overtly or subclinically, the chance for further hematogenous spread is great and the prognosis is poor for ultimate recovery without specific treatment.

Skin lesions are the most common metastatic manifestation of blastomycosis. As stated previously this was once thought to be a separate form of the disease but the work of several authors (Schwarz and Baum[116], Wilson *et al.*[148]) has definitely shown that almost all of the skin lesions seen in blastomycosis are secondary.

The reason(s) that Blastomyces metastasize to the skin so frequently is not known. The association of previous trauma to the appearance of skin lesions has led to many erroneous conclusions relating the trauma to the pathogenesis of the blastomycotic skin lesions. There are many other diseases where trauma calls attention to a preexisting but unnoticed lesion and this is often the case in blastomycosis. However, there are instances where lesions appear shortly after trauma so some association seems warranted. Many of these traumas are non-penetrating injuries so the development of a blastomycotic lesion at the site cannot be ascribed to the trauma alone. The creation of a locus minoris resistentiae may be responsible for the association of trauma and the appearance of skin lesions in blastomycosis.

J.B.: 54-year-old colored man who developed progressive cough with purulent sputum in April, 1950. There was associated weight loss of 37 pounds. In mid May, 1950, he noted pain, swelling and redness of the left ankle. He was hospitalized in late May and found to have rales in the chest and tenderness of the left ankle. Several sputa were negative for acid fast bacilli. Roentgen-ray revealed widespread nodularity of both lung fields. The lesion on the heel broke down and extruded a splinter supposedly picked up traumatically 6 months before. It did not heal. Soon there developed scattered pustular skin lesions and urinary obstruction. *Blastomyces dermatitidis* was seen in the prostatic secretions. Subsequently organisms were seen and grown from urine, sputum, and skin lesions. The patient progressively deteriorated and died on January 8, 1951. Necropsy revealed widespread disease. It is of interest that during hospitalization *B. dermatitidis* was cultured from the bed linens.

The clinical characteristics of the cutaneous lesions of blastomycosis have been described and reported by many authors (Blodi and Huffman[8], Cash[14], Curtis and Bocobo[24], Downing and Folan[27], Elliot, Wilt and Duggan[34], Gaumond[47], Howles and Black[61],

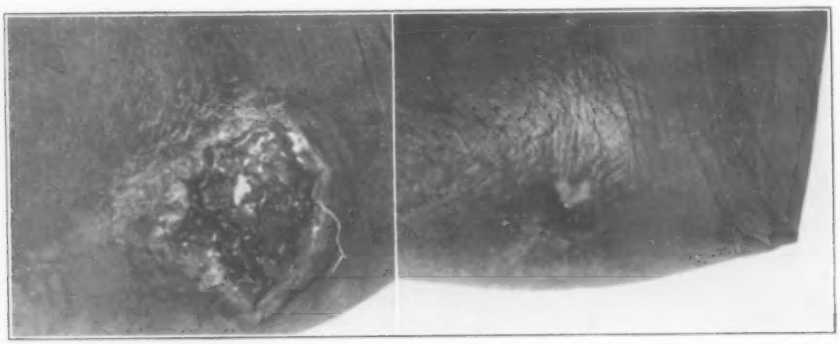

Fig. 5 Fig. 6

Fig. 5.—The skin lesions in blastomycosis are often ulcerative with indurated elevated borders which contain microabscesses, from which organisms can be easily aspirated for microscopic or cultural demonstration. 77-year-old Negro.

Fig. 6.—Same patient after amphotericin B (Fungizone) therapy.

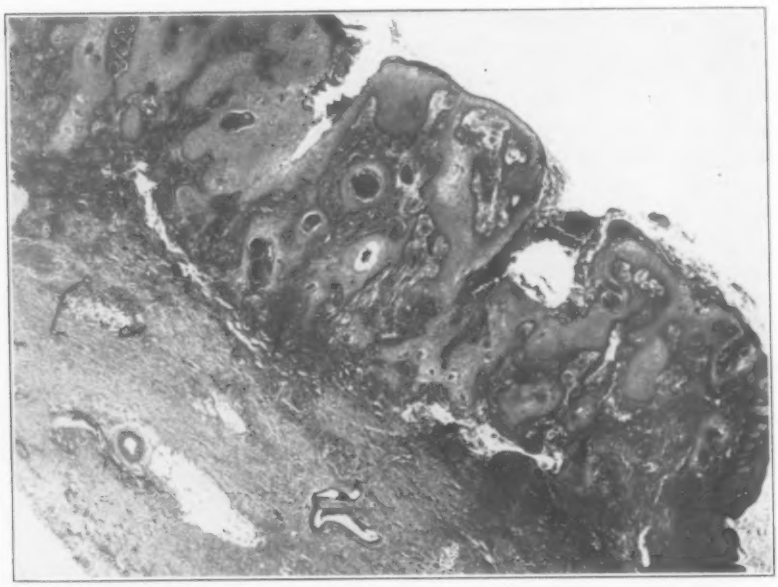

Fig. 7.—Microscopically the skin is characterized by a marked (pseudoepitheliomatous) thickening with intraepithelial microabscesses. Same patient 12×, H.E.

Leduc[72], Lehman and Ray[73], Macaulay[79], McClellan and Balowa[86], Poirier[102], Rattner, Rodin and Bielinski[104], Scott[122], Wilson *et al.*[148]).

In general there are two types of lesions seen: The ulcerating spreading lesion with evidence of micro-abscesses on the periphery and often with scarring in the center, and the subcutaneous abscess. There may be multiple cutaneous lesions or they may appear singly. Often there is a history of many different types of therapy having been used without lasting effect. There is usually slow progression in a centrifugal manner. The lesion may become disfiguring if allowed to go untreated long enough. There is noted central scarring in presence of peripheral micro-abscesses. From these pus may be obtained which reveals the organism on mount or culture, or both. Pain is rarely a clinical manifestation of significance unless there is an inordinate amount of scarring about well innervated areas or if there is a great amount of necrosis.

If there is activity of the pulmonary focus the skin lesions keep appearing at new sites and this more than any other point indicates the prognosis. If the pulmonary focus is arrested the only danger of the skin lesions is from local extension but if the pulmonary focus is active there is constantly a threat of generalized dissemination. The therapeutic implication of this is surgical removal of peripheral metastases (skin, bone) if the pulmonary focus is arrested. The only difficulty is the clinical uncertainty whether there is smoldering activity of the pulmonary lesion or not.

Involvement of the genitourinary tract is common in disseminated disease in men. This has been reported frequently in the literature (Burr and Huffines[13], Chick *et al.*[19], Cummins, Bairstow and Baker[23], Rolnick and Baumrucker[110], Schoenbach *et al.*[113], Schwarz and Baum[116], Tuttle, Lichtwardt and Altshuler[138], Watson, Moore and Blank[141]). Kidney, prostate and epididymis are the commonest sites of disease. The development of urinary retention secondary to a prostatitis is an occasional clinical expression of urinary tract blastomycosis. The urinary tract findings may be isolated manifestations of the disease or part of a generalized process. It has been suggested that secondary dissemination may occur from a prostatic abscess (Burr and Huffines[13]). Casts of Blastomyces in the kidney have been reported (Schwarz and Baum[116], Watson, Moore and Blank[141]).

Bone lesions have been reported in disseminated disease (Aszkanazy, Barrie and Crookston[3], Chick *et al.*[19], Cummins, Bairstow and Baker[23], Drummond and Smith[30], Elliot, Wilt and Duggan[34], Gagnon and Gelinas-Mackay[43], Thompson[135]). They are usually destructive and may appear punched out. We have observed one case in which there was isolated ankle involvement with no evidence of other foci of disseminated disease. With amputation the patient remained well (Schwarz and Baum[116]). As a rule the prognosis is poor since there is usually associated active disseminated disease.

The incidence of central nervous system involvement was 10% in one series of 40 cases (Cherniss and Waisbren[18]) and 3.75% in another of 80 cases (Chick *et al.*[19]). In one reported case an isolated spinal cord lesion was part of generalized dissemination (Tuttle, Lichtwardt and Altshuler[138]). Pituitary involvement has been observed (Watson, Moore and Blank[141]).

Another not uncommon site of involvement is the larynx (Ferguson[38], Lester, Conrad and Atwell[74], Stillians and Kemptner[131], Thornell[136]). This may represent extension of the pulmo-

nary disease rather than a true hematogenous focus. Involvement of the eyelids and retina (Blodi and Huffman[8], Sinskey and Anderson[124]), and the external auditory canal have been reported. The gastrointestinal tract has been remarkably free of disease in almost all reports but Chick and Sutliff[19] have reported one case as part of a generalized dissemination. Our own experience with over 50 cases has corroborated the rarity of this form of the disease.

In general the clinical manifestations of blastomycosis may be summarized as those of an indolent infection which is primary in the lung and which disseminates to all organs but predominantly the skin. The disease occurs much more frequently in men than in women but shows no recognizable predilection of races. The disease is rare in children and most common in the elderly. The ultimate prognosis in the untreated case depends on the activity of the pulmonary focus.

Treatment. Treatment of blastomycosis has only recently and for the first time become effective with the introduction of the aromatic diamidines (Editorial[33], Schoenbach and Greenspan[112]). Lately the introduction of amphotericin B has added another and possibly even a more effective agent (Harrell and Curtis[55]). Prior to this many drugs were used without consistent effect. The iodides are an "historical" medicine which, although never of lasting effect were used for decades in large doses for all types of blastomycosis. More recently undecylenic acid (Takero, Hopkins and Murphy[133]), aureomycin (McVay and Carroll[89]), diethylstilbestrol (Curtis and Harrell[26]) and iodides plus thyroid extract (Cummins, Bairstow and Baer[23]) have been used.

Stilbamidine (Blody and Huffman[8], Burr and Huffines[13], Cherniss and Waisbren[18], Cummins, Bairstow and Baker[23], Curtis and Bocobo[24], Curtis and Harrell[26], Fink, Vander Ploeg and Noursund[39], Forsey and Jackson[42], Harrell, Bocobo and Curtis[54], Knight and Wilson[66], Kuhn[68], Marx and Berenbaum[84], Myhr[97], Ostfield[100], Pariser, Levy and Rawson[101], Rolnick and Baumrucker[110], Schoenbach *et al.*[113, 114], Slaughter[125], Smith[126], Sutliff, Kyle and Hobson[132], Takero, Hopkins and Murphy[133]). and 2-hydroxystilbamidine (Colsky[21], Curtis and Bocobo[24], Grandbois *et al.*[50], Harrell, Bocobo and Curtis[54], London[76], Sattler and Marousek[111], Snapper and McVay[128], Steen, Foxworthy and Baker[130], Sutliff, Kyle and Hobson[132], Takero, Hopkins and Murphy[133]) have been given with fairly consistent success in all types of blastomycosis. There have been failures and recurrences (Curtis and Bocobo[24], Sattler and Marousek[111]) but in most instances the treatment has been attended by clinical arrest and for the first time patients with disseminated disease have improved because of treatment and not in spite of it. The chief drawback to these drugs is their toxicity. Stilbamidine is the more toxic of the two but this is only a quantitative difference. Because of the toxic implications the drug must be protected from light at all times including the period of administration by the intravenous route. Even so, 5th nerve damage is reported in a high percentage of cases and liver toxicity has been seen by us[117] and others to result rarely in death (Cohen[20]). Treatment must be carried out for many weeks in disseminated cases and response may be delayed for several weeks but in most cases arrest, at least temporarily, can be expected.

Amphotericin B, an antibiotic produced by a Streptomyces, has proven effective *in vitro* and *in vivo* against several of the deep fungi including

Blastomyces dermatitidis. Successful treatment of experimental blastomycosis with Amphotericin B was reported by Drouhet and Wilkinson[29]. The clinical experience with the drug is limited but it appears that this drug is at least as effective as the diamidines and considerably less toxic (Harrell and Curtis[55], Rebello[105]).

An 84-year-old white man was well until February, 1956, when he developed skin lesions on both heels. Subsequently he developed multiple skin lesions over his whole body and on the tongue. He had noted chronic mildly productive cough for many years. He was hospitalized in February, 1957, and lesions were noted on the tongue, cheek, ear, heels, and buttocks. Roentgenograms of the chest showed bilateral miliary infiltration. *Blastomyces dermatitidis* were found in the skin lesions. Treatment with intravenous amphotericin B resulted in excellent clearing of all lesions; with a dosage of 0.5 mg. per kg., intravenously for one month. Discharged on 1.0 gm. per day orally.

A 77-year-old colored man got a splinter of steel in the hypothenar area of his left hand in September, 1956. The splinter came out but the area did not heal and he developed an ulceration which was persistent. In March, 1957, he developed lesions on the nose and over both eyebrows. Chronic cough had been present for years. He was hospitalized in May, 1957, and the above lesions seen. In addition there was noted a right hilar infiltrate on chest roentgenogram. *Blastomyces dermatitidis* was cultured and seen in the skin biopsy material. Treatment was started with amphotericin B intravenously, 75 mg. per day for 20 days, and continued orally 3.0 gm. per day for 11 days in hospital and continued for about 2 months as an outpatient. There was dramatic clearing of all skin lesions to complete scarring. The lung lesions receded markedly.

Surgical therapy of skin lesions has been mentioned above (Levitas and Baum[75]) and again the activity of the pulmonary focus is the crucial point in determining whether removing the single skin lesion will be met with success or not. It is well to cover any such surgery with one of the drugs that are known to be effective.

SURGICAL THERAPY. Pulmonary resection has been invoked in the treatment of blastomycosis in occasional instances (Abraham and Luddecke[1], Acree, De Camp and Ochsner[2], Bueckner *et al.*[12], Campbell and Aronstam[16], Hopkins and Murphy[60], Kunkel *et al.*[69], Levitas and Baum[75], Matsumoto *et al.*[85], Sealy, Collins and Menefee[123], Takero, Hopkins and Murphy[133], Taylor[134], White and Owen[147]).

For many years iodides and desensitization were widely used and advocated in the treatment of blastomycosis. From the outset of the present authors'[116] experience it seemed clear that these therapeutic efforts were useless, in fact may have been harmful since the enormous doses of iodides given certainly may have caused iodide toxicity. The advent of the use of aromatic diamidines was an event of historical significance since an effective agent had finally been found for otherwise fatal disseminated blastomycosis. These drugs do not work permanently in every case and they are toxic but they are usually effective where all others before them were not. It would appear that at present amphotericin B will turn out to be the drug of choice since early experience with it has shown clinical effectiveness of a high order and less lasting toxicity (Baum, Schwarz and Wang[5], Harrell and Curtis[55]).

In the following table the results of our experience with various methods of treatment are summarized (See Table 1).

There are several interesting points brought out by this chart. Notice is immediately drawn to the first 2 cases which were treated by simple excision with excellent results. There are at least 4 other cases seen with skin lesions as the only manifestation clinically of their blastomycosis and although there has been no recent follow-up

they all did well for the short time that they were followed after the excisional treatment in 3 and use of iodides in one. During this same period there were several generalized cases (Schwarz and Baum[116]) that all died and at necropsy had widespread active disease. These cases had received iodides, Roentgen-ray, and excisional therapy for local lesions all of which were obviously ineffective. These cases must be contrasted with the generalized cases noted in the chart in whom diamidines and Amphotericin B resulted in clinical arrest with, in some cases several years follow-up. Therefore one can conclude that the localized skin lesion is a benign disease when there is no evidence of activity of other, especially pulmonary, foci. In these patients whatever is done will probably result in clinical arrest. However, the generalized active disease is lethal without effective treatment.

We have seen one case in which several courses of the diamidines were each effective but after variable periods the disease recurred (Case D.T.). It is interesting that the most recent treatment of this case, with amphotericin B seems to have produced a more marked clearing than the diamidines ever did.

TABLE 1.

Patient	*Age*	*Sex*	*Race*	*Clinical form*	*Treatment*	*Length*	*Follow-up result*
F.B.	65	M	W	skin lesion scalp	excision	46 months	no recurrence
J.G.	89	M	W	skin lesion thigh	excision graft	120 months	no recurrence
L.B.	36	M	W	skin lesion pleura and lung	2-HS*	53 months	no recurrence
E.M.	43	F	W	skin lesion and lung	2-HS and Stilbamidine	64 months	no recurrence
A.H.	7	M	N	skin lesion and lung	2-HS	21 months	no recurrence
J.E.	77	M	N	skin lesions and lung	Amphotericin B	6 months	no recurrence
D.T.	35	M	W	skin lesions and lung	Amphotericin B	3 months	no recurrence
J.N.	84	M	W	skin lesions and lung	Amphotericin B	5 months	no recurrence

*2-hydroxystilbamidine

EXPERIMENTAL THERAPY. *In vitro* studies of the effectiveness of six aromatic diamidines in inhibiting *Blastomyces dermatitidis* showed that at room temperature and at 37° C. amino stilbamidine was the most effective. The minimal inhibitory concentration of stilbamidine and 2-hydroxystilbamidine was the same at 37° C. but at room temperature stilbamidine was the more effective (McMillen, Kushner and Snapper[88]). Other reports have appeared corroborating the *in vitro* effectiveness of small concentrations of stilbamidine (Curtis and Harrell[26], Heilman[58]).

Several cinnamic acid derivatives were found not to be practical for clinical use (Curtis *et al.*[25]).

Protection of animals by varying doses of stilbamidine (Heilman[58],

Kingwest and Verwey[65]) and amphotericin B (Drouhet and Wilkinson[29]) against infection with *Blastomyces dermatitidis* has been demonstrated.

Diagnosis. The diagnosis of blastomycosis depends most on the awareness of the physician, in any given case, of the possibility that blastomycosis exists. There are many clinical suggestions that should prompt the use of certain laboratory aids so that a reasonable accuracy in the diagnosis will be achieved.

The presence of an indolent cutaneous lesion that resists any of the usual methods of treatment or suggests skin cancer should alert the clinician to the possibility of blastomycosis. The finding of centrifugal spread with microabscess formation is particularly suspicious. The presence of unexplained purulent prostatic secretions or sudden urinary obstruction with the finding of an enlarged, boggy prostate can suggest blastomycosis. Any form of chronic pulmonary inflammatory lesion with or without cavities which is not obviously tuberculous should be suspected of being fungal in etiology, in the Mideastern United States most probably blastomycotic or histoplasmic. The presence of destructive bone lesions, especially those resembling chronic osteomyelitis are possibly of blastomycotic etiology and should prompt search for the organism. Exceptionally even in cases of acute pneumonia where the etiology is not apparent, blastomycosis must be entertained in the differential diagnosis.

The only absolute diagnostic finding is a positive culture of the organism *Blastomyces dermatitidis*. This should be sought in every case. Almost as convincing is the finding of the organism on KOH mount of various specimens such as sputum, pus, prostatic secretions, urine, and others. This should be followed by culture verification as mentioned. Biopsy specimens offer diagnostic help when the organism is seen either in the H. and E. sections or in those stained with the special "fungus" stains such as the Gridley[51] or Grocott[52] procedures. Since confusion with other organisms may easily occur, especially among the inexperienced, the finding of characteristic budding, with broad base of the bud, of the suspected cells should be a *conditio sine qua non* of making the diagnosis either in histologic sections or in direct mounts.

At this point mention should be made of the small forms of *B. dermatitidis* since they cause confusion with *Histoplasma capsulatum* especially (Martin[81], Schwarz and Baum[116], Thompkins and Schleifstein[137], Wade and Bel[140], Weed[142]). On the other hand, under certain conditions *Histoplasma capsulatum* produces large forms which are indistinguishable from Blastomyces (of "normal" size) morphologically. These facts emphasize the crucial nature of culture in making the exact etiologic diagnosis (Moore[94]).

Though not conclusive the typical pathological anatomy of blastomycosis is most suggestive of the diagnosis when seen in skin biopsies. This consists of pseudo-epitheliomatous hyperplasia with intraepithelial micro abscess formation.

The combination of granulomatous inflammatory changes and significant polymorphonuclear leukocytic exudate is suspicious of blastomycosis. Again cultural corroboration is necessary to make the diagnosis definite.

In the absence of histologic or cultural evidence the diagnosis must sometimes be made conditionally on the basis of skin test and serologic data. A positive skin test in the absence of evidence of cross reaction with one of the other fungus antigens is highly suggestive of past or present blastomycosis.

Blastomyces dermatitidis is poorly antigenic for production of skin and complement fixing antibodies so that one may encounter active clinical disease with negative skin test and serologic reactions. The opposite situation is most unusual so the diagnostic significance of positive skin or serologic data, or both, for active disease, when the possibility of cross reaction has been ruled out, is great. However, if one depends on these data alone the diagnosis will be missed more than it will be made because of the above mentioned characteristic antigenic unresponsiveness.

No definite significance in prognosis of falling or persisting titer of serologic antibodies has been established. A rising titer of serologic antibodies is the best evidence of active disease that can be obtained with this method. Since there is a high degree of cross reaction with other fungus serologic antibodies (Campbell and Binkley[15]) one must be sure that the serologic findings are not due to one of the other deep fungus diseases, especially histoplasmosis. The simultaneous use of the skin test and the complement fixation test for blastomycosis, histoplasmosis and coccidioidomycosis is the wisest procedure.

Differential diagnosis of the skin lesions of blastomycosis includes carcinoma, syphilis, South American blastomycosis, histoplasmosis, coccidoidomycosis, cryptococcosis, nocardiosis, actinomycosis, tuberculosis, bromoderma, pyoderma, and others. In acute pulmonary lesions, virus pneumonia, acute histoplasmosis, acute coccidioidomycosis, bacterial bronchopneumonia, and tuberculosis must be ruled out. When chronic lesions are encountered, tuberculosis and the deep fungus diseases mentioned above plus sarcoid, eosinophilic pneumonia, periarteritis nodosa, disseminated lupus erythematosus and eosinophilic granuloma must be considered. It should be mentioned that blastomycosis is listed as one of the myriad causes of miliary pneumonia (Felson and Heublein[37], Hawley and Felson[57]). The finding of active generalized disseminated blastomycosis must be differentiated from tuberculosis, histoplasmosis, cryptococcosis, coccidioidomycosis, actinomycosis, nocardiosis, eosinophilic granuloma, staphylococcal septicemia and periarteritis nodosa.

Since there is a host of clinical conditions that simulate blastomycosis, the physician must be aware of the details that favor the diagnosis of this disease. These are mentioned in part above but two others should be emphasized. One is the almost complete lack of involvement of the gastrointestinal tract in North American blastomycosis and the other is the frequent association of minimal pulmonary lesions with occasional appearance of indolent skin lesions. One final point is the significance of geography in the finding of blastomycosis. For whatever the reasons the largest number of cases have been seen in the Mississippi-Ohio river valley including Wisconsin, Illinois, Ohio, Tennessee, North Carolina, and Michigan (Schwarz and Goldman[121]).

Mycology: *Blastomyces dermatitidis*, (Gilchrist and Stokes, 1898) is a biphasic fungus (belonging to the Fungi Imperfecti) which grows as a mold at room temperature (20° C.) on a variety of media and as a yeast at 37° C. best on media containing noncoagulated protein. This latter form is also known as the parasitic phase since the organism is seen in this form in infected human and animal tissues.

The mold (saprophytic, mycelial) phase grows slowly on Sabouraud's agar appearing in an average of one to 2 weeks after inoculation of the media. Heavy inocula may produce

growth in 5 or 6 days while minimal infection of tissue explants may take up to 6 weeks to produce growth. The colony is well circumscribed with a white cottony growth that appears early. It gradually enlarges centrifugally with continued aerial mycelium. This can gradually change from white to tan in color and ultimately to brown in colonies of several months age. Mount of a mold culture reveals branching septate hyphae of 1 to 2 micra width. Racquet hyphae may be present. A moderate number of microconidia are seen as are occasional chlamydospores. There is nothing grossly or microscopically which would differentiate this from *Histoplasma capsulatum* (young culture) or *Blastomyces brasiliensis*, two organisms which produce disease which may be clinically similar to North American blastomycosis.

The yeast (tissue, parasitic) phase of Blastomyces grows on uncoagulated protein containing media such as blood agar, egg medium (Kurung and Yegian[70]), brain, heart infusion and the like. It must be incubated at 37° C., the inoculation must be heavy and the culture should be sealed. In 3 to 5 days warty tan to grey colonies appear which grow slowly and look somewhat dry. Mount reveals roughly round cells, 8 to 24 micra in diameter with thick walls and lipid bubbles within the cells. According to Emmons[36] and Bakerspigel[6] the yeast cell

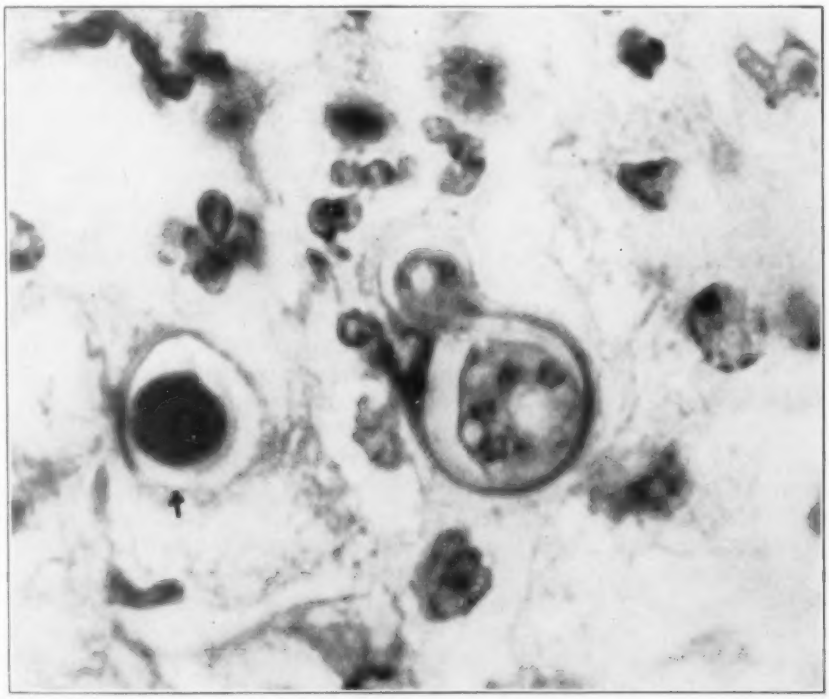

Fig. 8.—Blastomyces dermatitidis. The organism is thick walled, 8 to 24 μ large (in average) with single buds which are attached by a broad base. The second organism is not budding, 300 ×.

of *B. dermatitidis* is multinucleated. Budding is noted and is characteristically single. In addition the base of the bud is broad, a diagnostic point. Hyphal remnants of the original inoculum may be noted.

B. dermatitidis grows on a variety of media at room temperature with a pH range from 4.1 to 7.5 (Moore[93]). Biotin appears to be a growth requirement of importance (Halliday and McCoy[53]). Trimeton maleate and pyribenzamine in high concentration inhibit *in vitro* growth of the organisms (Gale[45], Reiss and Caroline[106,107]). Pyribenzamine in low concentrations seems to enhance the growth (Gale[45]); propiolactone inhibits metabolism *in vitro* (Gale[44]).

Immunology. Dyson and Evans[31,32] have used ethanol to precipitate yeast phase cultures of *Blastomyces dermatitidis* and from the supernatant they have extracted a polysaccharide which apparently is a specific antigen when used in skin testing in rabbits. They encountered no cross reactions with the material.

Martin[81,82] obtained two antigens from the yeast cell of *Blastomyces dermatitidis;* one, a polysaccharide from the surface of the cell which was reflected in a hemagglutination test and another, a protein from within the cell, which was reflected in the complement-fixation test. There was no quantitative relationship between the two antigens.

Discussion. North American blastomycosis is interesting to the clinician, the pathologist and the epidemiologist and because of this varied appeal the work done on this disease has led to several different approaches to the problem.

From clinical evaluation of the cases observed several generalizations seem warranted. Blastomycosis is primarily a chronic, indolent active infection that rarely becomes acute and rapidly progressive. The most commonly observed clinical manifestation is the skin lesion. It may appear as a single focus of the disease or may be accompanied by many sister skin lesions in various stages of development. Finally the skin lesions may be a part of active disseminated disease with simultaneous lesions of many internal organs as well as of the skin. The one common factor in all variations of the skin manifestations of blastomycosis is that the primary lesion is in the lung and all the lesions seen, whether localized to the skin or spread throughout the body, are metastatic. For unknown reasons the gastrointestinal tract is spared in blastomycosis. In some of the other deep fungus diseases, like histoplasmosis and especially in South American blastomycosis the gastrointestinal tract is a common site of involvement so that this point can become helpful in differential diagnosis.

Pulmonary blastomycosis, despite being the primary lesion in all types of blastomycosis is often clinically silent. There may be no obvious pulmonary focus on clinical or roentgenographic examination or the roentgenogram may reveal a nondescript scar or thickening. This point is most often used by those who feel that blastomycosis is not a primary pulmonary disease but one has merely to think of the innumerable cases of renal, bone, or meningeal tuberculosis in which no pulmonary focus is visible clinically or by Roentgen-ray to realize that this grossness of clinical or roentgenographic examination has nothing to do with pathogenetic principles. Certainly it is established beyond doubt that the above types of tuberculosis are secondary to pulmonary foci. For the same reasons peripheral blastomycosis is secondary to a primary pulmonary lesion whether the pulmonary lesion is clinically discernable or not.

On occasion pulmonary blastomyco-

sis becomes a clinical entity. It may exist as an acute or chronic pulmonary disease with no associated remote lesions or it may be a part of a clinically disseminated disease process. The least frequently seen type of pulmonary manifestation is the acute pneumonic form which is indistinguishable from any other type of acute pneumonia. This was observed in the epidemic reported by Smith *et al.*[56,127]. Of interest is the fact that in several other chronic pulmonary diseases (tuberculosis, histoplasmosis, coccidioidomycosis) asymptomatic pulmonary infection has been proposed on the basis of positive skin reactions in patients who had no history of active disease. With increased clinical awareness, this situation was in fact seen; but despite the obvious clinical similarity, asymptomatic pulmonary blastomycosis has actually not been observed, though it probably occurs sporadically.

The chronic form of pulmonary blastomycosis is nonspecific in clinical or roentgenographic appearance. The wide range of the roentgenographic findings has been noted by Hawley and Felson[57] and the nonspecificity of the clinical syndrome is well known. The diagnosis will be missed frequently unless the observers of this type of disease recognize the widely variable nature of the possible causes.

The pathologic picture of blastomycosis combines an acute purulent reaction with a chronic granulomatous one in most of the organs where the disease is observed. In the lung this produces a reaction which in part is similar to tuberculosis and the other deep fungus diseases (coccidioidomycosis, histoplasmosis, torulosis) and a response which is different from any of them. The former is, of course, the development of epithelioid cell granulomata which, except for the presence of the specific organism, are similar in the diseases mentioned. The latter is micro-abscess formation which is commonly found in blastomycosis and not in the other entities. This is seen in all organs and has particular expression in the skin where the abscesses are visible and serve as sources for diagnostic material and in the prostate where abscess formation may lead to urinary obstruction. One reaction that is not specially prominent in blastomycosis is caseation necrosis (Weed[143]).

Biopsies, especially from the scalene fat pad, lymph nodes, and lung, have resulted in the diagnosis of all of the fungus diseases more often than previously. Along with the increased material have come more effective methods for visualizing the organism, particularly the so-called "fungus stains." These include the Gridley[51], Grocott[52], the PAS and the Bauer stains. Because these stains merely bring out the chitinous wall of the organism, the morphologic detail seen with hematoxylin and eosin is lost for the most part and except in unusual instances cultural verification is needed to make an etiologic diagnosis.

It is in the sphere of epidemiology that the large void in present knowledge is apparent. Geographic variation in incidence of this disease has been observed (Schwarz and Goldman[121]). A *bona-fide* epidemic has been reported with skin test survey of the entire area of the epidemic (Harris *et al.*[56,127]). Much indirect evidence exists that the disease is acquired by inhalation of the spores of the mold phase of *Blastomyces dermatitidis* existing in soil but the organism has not yet been recovered naturally from the soil. It has been shown that sterilized soil will support the growth of *B. dermatitidis* (Emmons[35]) but no one has as yet been able to culture the organism from collected material; even when contamination of a high order was known to have

occurred. It stands to reason that the organism must exist in some reservoir and that our inability to culture it most likely represents some technical error rather than some exotic behavior of the organism.

Finally one must mention the therapy of blastomycosis since it has been one of the goals of all the careful work which has attempted to emphasize the importance of diagnosing this condition and understanding it. The aromatic diamidines are effective treatment but have had many undesirable side effects. In the last few years there has been evidence that these drugs are not 100% curative (Harrell, Bocobo and Curtis[54]). Recently amphotericin B, the product of a Streptomyces, has been shown to be effective against *Blastomyces dermatitidis*. Amphotericin B is a relatively safe and effective agent for the treatment of blastomycosis and must be considered the treatment of choice until replaced by some even better new agent.

Summary. In summary one can say that North American blastomycosis is an almost conquered disease. The excellent response to amphotericin B and in many cases to stilbamidine and its derivatives has removed the fear of the diagnosis of this disease and contrasts most favorably with the therapeutic impotence before 1951. There is little doubt that in the near future new therapeutic tools will bring even better results.

One of the major problems which awaits solution is the peculiar geographical distribution of the disease, and the enigma concerning the natural source of the organism *Blastomyces dermatitidis*.

The disease in most cases is pulmonary in origin but the organism is definitely dermotropic and cutaneous involvement is common. This, however, should not be confused with the exceptional cases of primary cutaneous inoculation, which so far have been observed only in laboratory workers.

There is no proof of transmission of blastomycosis from man to man, or animal to man. There seem to be few, if any, sub-clinical infections.

In North America the disease should be suspected in all chronic pulmonary disorders of granulomatous character which are not tuberculous, histoplasmic or of other mycotic origin. Even when tumor is suspected from roentgenograms, blastomycosis should not be counted out.

In cutaneous blastomycosis bromoderma is a source of error, as are epitheliomatous skin tumors and granulomata of different etiology.

Awareness of the possibility of blastomycosis and search for the organism *Blastomyces dermatitidis* will obviate mistakes in diagnosis and lead to effective therapy.

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REFERENCES

1. **Abraham, A.**, and **Luddecke, H. F.**: Dis. Chest, **28**, 687, 1955.
2. **Acree, P. W., De Camp, P. T.**, and **Ochsner, A.**: J. Thoracic Surg., **28**, 175, 1954.
3. **Aszkanazy, C. L., Barrie, H. J.**, and **Crookston, J. H.**: Canad. Med. Assn. J., **65**, 55, 1951.
4. **Baker, R. D., Warrick, G. W.**, and **Noojin, R. O.**: A.M.A. Arch. Int. Med., **90**, 718, 1952.
5. **Baum, G. L., Schwarz, J.**, and **Wang, C. J. K.**: Ibid., **101**, 54, 1958.
6. **Bakerspigel, A.**: Canad. J. Microb., **3**, 923, 1957.
7. **Black, T. C.**, and **Wilson, H. M.**: Am. Rev. Tuberc., **68**, 615, 1953.

8. **Blodi, F. C.,** and **Huffman, W. C.:** A.M.A. Arch. Ophth., **59,** 459, 1958.
9. **Bonoff, C. P.:** Radiology, **54,** 157, 1950.
10. **Borelli, D.:** Hautarzt, **7,** 329, 1956.
11. **Brody, M.:** A.M.A. Arch. Dermat. & Syph., **56,** 529, 1947.
12. **Bueckner, H. A., Anderson, A. E., Strug, L. E., Seabury, J. H.,** and **Peabody, J. W., Jr.:** J. Thoracic Surg., **25,** 468, 1953.
13. **Burr, A. H.,** and **Huffines, T. R.:** J. Urol., **71,** 464, 1954.
14. **Cash, R. C.:** J. Kentucky Med. Assn., **49,** 110, 1951.
15. **Campbell, C. C.,** and **Binkley, G. E.:** J. Lab. & Clin. Med., **42,** 896, 1953.
16. **Campbell, R. E.,** and **Aronstam, E. M.:** Dis. Chest, **30,** 576, 1956.
17. **Chasen, W.:** Riv. ital stomat., **6,** 1040, 1951.
18. **Cherniss, E. I.,** and **Waisbren, B. A.:** Ann. Int. Med., **44,** 105, 1956.
19. **Chick, E. W., Sutliff, W. D., Rakich, J. H.,** and **Furcolow, M. L.:** Am. J. Med. Sci., **231,** 253, 1956.
20. **Cohen, R.:** J. Am. Med. Assn., **150,** 1332, 1952.
21. **Colsky, J.:** A.M.A. Arch. Int. Med., **93,** 796, 1954.
22. **Cornbleet, T.:** A.M.A. Arch. Dermat., **76,** 545, 1957.
23. **Cummins, C. R., Bairstow, B.,** and **Baker, L. A.:** A.M.A. Arch. Int. Med., **92,** 98, 1953.
24. **Curtis, A. C.,** and **Bocobo, F. C.:** J. Chron. Dis., **5,** 404, 1957.
25. **Curtis, A. C., Bocobo, F. C., Harrell, E. R.,** and **Block, W. D.:** A.M.A. Arch. Dermat., **70,** 786, 1954.
26. **Curtis, A. C.,** and **Harrell, E. R.:** Ibid., **60,** 676, 1952.
27. **Downing, J. G.,** and **Folan, D. W.:** New England J. Med., **252,** 103, 1955.
28. **Drouhet, E.:** Personal communication.
29. **Drouhet, E.,** and **Wilkinson, R.:** Ann. Inst. Pasteur, Par., **93,** 631, 1957.
30. **Drummond, K. L.,** and **Smith, J. D.:** Canad. Med. Assn. J., **63,** 598, 1950.
31. **Dyson, J. E.,** and **Evans, E. E.:** Univ. Michigan Med. Bull., **20,** 53, 1954.
32. Iidem: J. Invest. Dermat., **24,** 447, 1955.
33. Editorial: J. Am. Med. Assn., **154,** 588, 1954.
34. **Elliot, G. B., Wilt, J. C.,** and **Duggan, M.:** Canad. Med. Assn. J., **67,** 650, 1952.
35. **Emmons, C. W.:** Tr. New York Acad. Sci., **14,** 51, 1951.
36. **Emmons, C. W.:** Proceedings of Histoplasmosis Seminar, p. 5, Cincinnati, Ohio, February, 11, 1958.
37. **Felson, H.,** and **Heublein, G. W.:** Am. J. Roentgenol., **59,** 59, 1948.
38. **Ferguson, G. B.:** Laryngoscope, **61,** 851, 1951.
39. **Fink, J. C., Vander Ploeg, D. E.,** and **Moursund, M. P.:** J. Am. Med. Assn., **151,** 1395, 1953.
40. **Foldvari, F.,** and **Florian, E.:** Orv. hetil., **95,** 85, 1954.
41. Iidem: Hautarzt, **6,** 294, 1955.
42. **Forsey, R. R.,** and **Jackson, R.:** A.M.A. Arch. Dermat., **68,** 89, 1953.
43. **Gagnon, E. D.,** and **Gelinas-Mackay, C.:** Union méd. Canada, **80,** 753, 1951.
44. **Gale, G. R.:** J. Bact., **65,** 505, 1953.
45. Idem: Antibiotics and Chermother., **4,** 33, 1954.
46. **Garcia, F. E.,** and **Ledesma, R.:** Rev. clin. espan., **50,** 56, 1953.
47. **Gaumond, E.:** Laval méd., **18,** 1319, 1953.
48. **Gilchrist, T. C.,** and **Stokes, W. R.:** Bull. Johns Hopkins Hosp., **7,** 129, 1896.
49. **Giroux, M.,** and **Dessureault, R.:** Laval méd., **20,** 1326, 1955.
50. **Grandbois, J., Giroux, M., Gavel, J.,** and **Beaulieu, M.:** Ibid., **24,** 165, 1957.
51. **Gridley, M. F.:** Am. J. Clin. Path., **23,** 303, 1953.
52. **Grocot, R. G.:** Ibid., **25,** 975, 1955.
53. **Halliday, W. J.,** and **McCoy, E.:** J. Bact., **70,** 464, 1955.
54. **Harrell, E. R., Bocobo, F. C.,** and **Curtis, A. C.:** Ann. Int. Med., **43,** 1076, 1955.
55. **Harrell, E. R.,** and **Curtis, A. C.:** A.M.A. Arch. Dermat., **76,** 561, 1957.
56. **Harris, J. S., Smith, J. G., Jr., Humbert, W. C., Conant, N. F.,** and **Smith, D. T.:** Pub. Health Rep., **72,** 95, 1957.
57. **Hawley, C.,** and **Felson, B.:** Am. J. Roentgenol., **75,** 751, 1956.
58. **Heilman, F. R.:** Proc. Staff Meet., Mayo Clinic, **27,** 455, 1952.
59. **Helmig, H.:** Helvet. chir. acta, **24,** 387, 1957.
60. **Hopkins, J. E. T.,** and **Murphy, J. D.:** J. Thoracic Surg., **23,** 409, 1952.
61. **Howles, J. K.,** and **Black, C. I.:** J. Louisiana Med. Soc., **105,** 72, 1953.

62. **Jayaram, S. S., Sirsi, M., Ahmed, V. N.,** and **Dayalu, T. K.**: J. Indian Med. Assn., **21**, 365, 1952.
63. **Joulia, P.,** and **Le Coulant**: Maroc. méd., **34**, 572, 1955.
64. **Keller, A. P.,** and **Meissner, T. O. W.**: A.M.A. Arch. Otolaryng., **53**, 296, 1951.
65. **Kingwest, M.,** and **Verwey, W. F.**: J. Invest. Dermat., **22**, 363, 1954.
66. **Knight, V. H.,** and **Wilson, W. W.**: J. Florida Med. Assn., **42**, 275, 1955.
67. **Kovacs, A.**: Orv. hetil., **97**, 1145, 1956.
68. **Kuhn, B. H.**: A.M.A. Arch. Dermat., **73**, 556, 1956.
69. **Kunkel, W. M., Weed, L. A., McDonald, J. R.,** and **Clagett, O. T.**: Surg. Gynec. & Obst., **99**, 1, 1954.
70. **Kurung, J. M.,** and **Yegian, D.**: Am. J. Clin. Path., **24**, 505, 1954.
71. **Layton, J. M., McKee, A. P.,** and **Stamler, F. W.**: Ibid., **23**, 904, 1953.
72. **Leduc, A.**: Union méd. Canada, **82**, 282, 1953.
73. **Lehman, W. L.,** and **Ray, L. F.**: Northwest Med., **50**, 39, 1951.
74. **Lester, C. F., Conrad, F. G.,** and **Atwell, R. J.**: Am. J. Med., **24**, 305, 1958.
75. **Levitas, J. R.,** and **Baum, G. L.**: Surgery, **33**, 93, 1953.
76. **London, L. D.**: South. Med. J., **49**, 1098, 1956.
77. **Lövei, E.,** and **Bogsch, A.**: Fortschr. Geb. Röntgenstrahlen, **81**, 449, 1954.
78. **Lucasse, C., Duquenoy, J. J.,** and **Otten, A. E.**: Ann. Soc. belge med. trop., **37**, 647, 1957.
79. **Macaulay, W. L.**: A.M.A. Arch. Dermat., **73**, 560, 1956.
80. **Manwaring, J. H.**: A.M.A. Arch. Path., **48**, 421, 1949.
81. **Martin, D. S.**: J. Immunol., **71**, 192, 1953.
82. Idem: Pub. Health Monographs, **39**, 166, 1956.
83. **Martinez, B. M., Reyes, M. A.,** and **Gonzales Ochoa, A.**: Rev. Inst. salub. y enferm. trop., **14**, 225, 1954.
84. **Marx, F. J.,** and **Berenbaum, A. A.**: New England J. Med., **251**, 56, 1954.
85. **Matsumoto, K. K., Amatuzio, D. S., Lomasney, T. L., Ayres, W. W.,** and **Cuttle, T. D.**: Am. J. Med. Sci., **229**, 172, 1955.
86. **McClellan, J. T.,** and **Balowa, A.**: J. Kentucky Med. Assn., **52**, 855, 1954.
87. **McMillan, H.**: Australian J. Dermat., **3**, 38, 1955.
88. **McMillen, S., Kushner, D. S.,** and **Snapper, I.**: J. Invest. Dermat., **24**, 455, 1955.
89. **McVay, L. V.,** and **Carroll, D. S.**: Am. J. Med., **12**, 289, 1952.
90. **Menges, R. W., Furcolow, M. L., Larsh, H. W.,** and **Hinton, A.**: J. Infect. Dis., **90**, 67, 1952.
91. **Monod, R.,** and **Mahassen, M.**: Poumon & Coeur, **11**, 285, 1955.
92. **Montemayor, L.**: Gac. méd. Caracas, **62**, 675, 1954.
93. **Moore, M.**: Ann. Missouri Botan. Garden, **20**, 79, 1933.
94. Idem: Am. J. Path., **31**, 1049, 1955.
95. **Muller, E.,** and **Hilscher, W. M.**: Zentralbl. allg. Path., **92**, 331, 1954.
96. **Muray, M.**: Gyermekgyogyaszat, **6**, 378, 1955.
97. **Myhr, L. B.**: Am. Pract. & Digest Treat., **5**, 64, 1954.
98. **Newberne, J. W., Neal, J. E.,** and **Heath, M. K.**: J. Am. Vet. Med. Assn., **127**, 220, 1955.
99. **O'Donoghue, J. G.**: Med. J. Australia, **1**, 118, 1933.
100. **Ostfield, A. M.**: Am. J. Med., **15**, 746, 1953.
101. **Pariser, H., Levy, E. D.,** and **Rawson, A. J.**: J. Am. Med. Assn., **152**, 129, 1953.
102. **Poirier, P.**: Union méd. Canada, **84**, 287, 1955.
103. **Polo, F. J., Brass, K.,** and **De Montemayor, L.**: Rev. san. Caracas, **19**, 217, 1954.
104. **Rattner, H., Rodin, H.,** and **Bielinski, S.**: A.M.A. Arch. Dermat. & Syph., **68**, 221, 1953.
105. **Rebello, D. J. A.**: Ind. J. Dermat., **3**, 133, 1958.
106. **Reiss, F.,** and **Caroline, L.**: Science, **114**, 15, 1951.
107. Iidem: A.M.A. Arch. Dermat., **71**, 500, 1955.
108. **Robbins, E. S.**: J. Am. Vet. Med. Assn., **125**, 391, 1954.
109. **Robinson, V. B.,** and **Schell, F. G.**: North Am. Vet., **32**, 555, 1951.
110. **Rolnick, D.,** and **Baumrucker, G. O.**: J. Urol., **79**, 315, 1958.
111. **Sattler, T. H.,** and **Marousek, M. A.**: South Dakota J. Med. & Pharm., **9**, 325, 1956.
112. **Schoenbach, E. B.,** and **Greenspan, E. M.**: Medicine, **27**, 327, 1948.
113. **Schoenbach, E. B., Miller, J. M., Ginsberg, M.,** and **Long, P. H.**: J. Am. Med. Assn., **146**, 1317 1951.

114. **Schoenbach, E. B., Miller, J. M.,** and **Long, P. H.:** Ann. Int. Med., **37,** 31, 1952.
115. **Schoenmackers, J.:** Zentralbl. allg. Path., **87,** 441, 1951.
116. **Schwarz, J.,** and **Baum, G. L.:** Am. J. Clin. Path., **21,** 999, 1951.
117. Iidem: J. Invest. Dermat., **18,** 3, 1952.
118. Iidem: Docum med. geog. et trop., **5,** 29, 1953.
119. Iidem: Radiology, **61,** 818, 1953.
120. Iidem: A.M.A. Arch. Dermat., **71,** 143, 1955.
121. **Schwarz, J.,** and **Goldman, L.:** Ibid., **71,** 84, 1954.
122. **Scott, M. J.:** Northwest Med., **54,** 255, 1955.
123. **Sealy, W. C., Collins, J. P.,** and **Menefee, E. E.:** J. Thoracic Surg., **27,** 238, 1954.
124. **Sinskey, R. M.,** and **Anderson, W. B.:** A.M.A. Arch. Ophth., **54,** 602, 1955.
125. **Slaughter, J. C.:** A.M.A. Arch. Dermat. & Syph., **70,** 663, 1954.
126. **Smith, D. T.:** GP, **8,** 69, 1953.
127. **Smith, J. G., Harris, J. S., Conant, N. F.,** and **Smith, D. T.:** J. Am Med. Assn., **158,** 641, 1955.
128. **Snapper, I.,** and **McVay, L. W.:** Am. J. Med., **15,** 603, 1953.
129. **Snekszer, M.:** Börgyógy. vener. szemle, **11,** 124, 1957.
130. **Steen, L. H., Foxworthy, D. T.,** and **Baker, L. A.:** A.M.A. Arch. Int. Med., **93,** 464, 1954.
131. **Stillians, A. W.,** and **Klemptner, H. E.:** J. Am. Vet. Assn., **153,** 560, 1953.
132. **Sutliff, W. D., Kyle, J. W.,** and **Hobson, J. L.:** Ann. Int. Med., **41,** 89, 1954.
133. **Takero, T., Hopkins, J. E. T.,** and **Murphy, J. D.:** Dis. Chest, **28,** 203, 1955.
134. **Taylor, E. R.:** J. South Carolina Med. Assn., **52,** 128, 1956.
135. **Thompson, W. F.:** J. Bone & Joint Surg., **35,** 777, 1953.
136. **Thornell, W. C.:** Tr. Am. Laryngol. Assn., **76,** 184, 1955.
137. **Thompkins, V.,** and **Schleifstein, J.:** A.M.A. Arch. Path., **55,** 432, 1953.
138. **Tuttle, J. G., Lichtwardt, H. E.,** and **Altshuler, C. H.:** Am. J. Clin. Path., **23,** 890, 1953.
139. **Vermeil, C., Gordeef, A.,** and **Haddad, N.:** Ann. Inst. Pasteur, **86,** 636, 1954.
140. **Wade, H. W.,** and **Bel, S. A.:** A.M.A. Arch. Int. Med., **18,** 103, 1916.
141. **Watson, S. H., Moore, S.,** and **Blank, F.:** Canad. Med. Assn. J., **78,** 35, 1958.
142. **Weed, L. A.:** Am. J. Clin. Path., **23,** 921, 1953.
143. Idem: Ibid., **25,** 37, 1955.
144. **Wegman, T.:** Deutsches Arch. klin. Med., **199,** 192, 1952.
145. **Weinberg, B. J., Lawrence, C. H.,** and **Buckholz, A.:** A.M.A. Arch. Int. Med., **94,** 493, 1954.
146. **Weisel, W.,** and **Landis, F. B.:** J. Thoracic Surg., **25,** 570, 1953.
147. **White, M. L.,** and **Owen, E. T.:** Am. Surgeon, **20,** 981, 1954.
148. **Wilson, J. W., Cowley, E. P., Weidman, F. D.,** and **Gilmer, W. S.:** A.M.A. Arch. Dermat., **71,** 39, 1955.

SUMMARIO IN INTERLINGUA

Blastomycosis Nord-American

Blastomycosis nord-american es un morbo quasi conquerite. Le excellente responsa a amphotericina B e in multe casos a stilbamidina e su derivatos ha eliminate le terror del diagnose de iste morbo e forma un favorabile contrasto con le impotentia therapeutic ante le anno 1951. Il ha pauc dubita que in le proxime futuro nove medios therapeutic va producer resultatos ancora melior.

Un del principal problemas que attende su solution es le peculiaritate del distribution geographic de iste morbo e le enigma del fonte natural del organismo *Blastomyces dermatitidis*.

In le majoritate del casos le morbo es de origine pulmonar, sed le organismo es definitemente dermotropic, e affectiones cutanee es commun. Sed isto non debe esser confundite con le casos exceptional de primari inoculation cutanee que—usque nunc—ha essite observate solmente in personal laboratorial.

Il existe nulle prova del transmission de blastomycosis ab un homine al altere o ab animales a homines. Il occurre pauc, o nulle, infectiones sub-clinic.

In Nord-America, le morbo debe esser suspicite in omne casos de chronic disordine pulmonar de character granulomatose que non es de origine tuberculotic, histoplasmic, o alteremente mycotic. Mesmo in casos in que un tumor es suspicite super le base del roentgenogrammas, blastomycosis non pote esser considerate como excludite.

In blastomycosis cutanee, bromoderma es un fonte de error. Le mesmo es ver pro epitheliomatose tumores cutanee e granulomas de differente etiologias.

Esser conscie del possibilitate de blastomycosis e effortiar se a deteger le organismo *B. dermatitidis* evita errores diagnostic e resulta in un therapia efficace.

SUMMARIO IN INTERLINGUA

(See page 691 for original article)

Substantia Bioplastic
Le Signification del Substantia Fundamental Intercellular

Le substantia fundamental intercellular exerce importante functiones. Iste materia amorphe es pauco impressionante in preparatos histologic observate con le microscopio a lumine. Mucopolysaccharidos acide es prominente constituentes del substantia intercellular. Illos include acido hyaluronic e acido chondroitic. Iste amino-sucros se trova usualmente in combination con proteinas, le mucoproteinas. Acido hyaluronic es un polymero de N-acetylglucosamina e acido glucuronic. In sulfato de chondroitina, N-acetylgalactosamina es trovate insimul con acido glucuronic. Le anticoagulante heparina es etiam un amino-sucro. Illo es glucosamina N-sulfamatic e acido glucuronic.

Le pelle de humanos adulte contine circa 0,3% de polysaccharidos, e le sulfato de chondroitina excede per pauco le acido hyaluronic. In le pelle del embryo, ille procentage es circa 0,5, e acido hyaluronic predomina. Un vulnere in restauration resimila histos embryonic. Le metabolismo es intense. Le periodo del medie valor pro acido hyaluronic in le pelle es solmente 2 dies. Le administration de cortisona reduce le formation de hyaluronato in le histos sed augmenta le grado de polymerisation. Disoxycorticosterona augmenta le formation de hyaluronato.

Le substantia fundamental intercellular exerce multiple functiones. In le liquido synovial, un mucoproteina componite de acido hyaluronic e globulina gamma servi como lubricante pro le superficies articular. Cartilagine o le humor vitree del oculo es exemplos pro le function de supporto mechanic exercite per le amorphe substantia intercellular. Le materia interstitial servi como barriera contra le passage de liquidos o de particulas per le histos. Le injection de hyaluronidase o de partialmente dispolymerisate acido hyaluronic resulta in un alteration del permeabilitate del histos. In le transporto active de iones ab un cellula al altere, le mucopolysaccharidos functiona como excambiatores de iones. In le histos e in le urina le mucopolysaccharidos age como agentes de dispersion e augmenta le solubilitate de crystalloides.

POLIOMYELITIS IN INFANCY AND CHILDHOOD*

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Ensuing the first description in the medical press of poliomyelitis nearly a century ago, several thousand reports have been published on the virology, epidemiology, treatment, and prevention of this disease. A review of this voluminous literature revealed that, whereas most aspects of poliomyelitis have been thoroughly investigated and reported, there have been only a few reports on the variability of the clinical pattern and cerebrospinal fluid changes in poliomyelitis at different age levels. Inasmuch as most of these reports have been based on relatively small numbers of poliomyelitis cases, no clear conclusion could be derived from them whether there is a difference in the clinical picture and in the cerebrospinal fluid changes in different age groups.

The authors believe that the present report should be of interest, dealing, as it does, with 1,489 cases of poliomyelitis in infants and children, 1 month to 14 years of age, treated at Rambam Government Hospital and observed by the same persons.

Patient Material. In 1950, the outbreak of a poliomyelitis epidemic became apparent in Israel. All diagnosed cases of poliomyelitis were hospitalized at hospitals specially designated for this purpose. In northern Israel poliomyelitis patients were hospitalized at Rambam Government Hospital in Haifa.

During the following 7-year period up to the end of 1956, 1,489 infants and children with poliomyelitis were treated at Pediatric Department B of this hospital. A detailed history was obtained from the parents of each patient in an attempt to evaluate the first signs and symptoms of the disease. Every effort was made to acquire accurate information and to eliminate any erroneous data from this study. Patients were hospitalized usually for 3 weeks. The more severe cases requiring artificial respiration or specialized orthopedic care remained for longer periods.

Of the 1,489 patients which serve as the basis of this report, 1,282 had paralytic poliomyelitis; 207 had non-paralytic poliomyelitis. Of the paralytic cases, 879 were spinal type cases, 149 were bulbar, facial or encephalitic type; the remaining 254 patients presented signs of involvement of both spinal cord nuclei and bulbar nuclei.

The patients were grouped in four age groups: *early infancy group* comprised of patients younger than one year of age; *late infancy group*, comprised of patients 13 to 24 months old; *early childhood group*, in which patients 3 to 6 years of age were included; and, *late childhood group*, comprised of patients 7 to 14 years old. The distribution of 1,489 poliomyelitis patients in the four age groups is presented in Table 1.

Description of Clinical Data. Two major clinical signs were considered: the presence of signs of meningeal irritation and the number of days between the onset of the disease and the appearance of muscular weakness or signs of bulbar nuclei involvement.

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Signs of meningeal irritation were considered to be present when either neck stiffness, Kernig's sign, or Brudzinski's sign were found, alone or together. In infants a bulging anterior fontanel was as well considered a sign of meningeal irritation. On the other hand, the presence of a Brudzinski's sign was not considered necessarily pathological in *early infancy*. Therefore, when only a positive Brudzinski's sign was elicited in a patient belonging to the *early infancy group*, he was included in a third group entitled: Meningeal irritation signs doubtful.

The distribution of the poliomyelitis patients in the different age groups according to the presence or absence of signs of meningeal irritation is presented in Table 2.

The distribution of the 1,282 paralytic cases of poliomyelitis according to the number of days after the onset of the acute disease when muscle weakness, signs of bulbar nuclei involvement or encephalopathy, or both, were first observed is presented in Table 3.

TABLE 1.—DISTRIBUTION OF POLIOMYELITIS CASES IN DIFFERENT AGE GROUPS

Age group	*No. of cases*	*% of total number*
Early infancy*	529	36
Late infancy†	510	34
Early childhood‡	397	26
Late childhood§	53	4
Total	1,489	100

*Less than one year of age
†2 years of age
‡3 to 6 years of age
§7 to 14 years of age

TABLE 2.—FREQUENCY OF SIGNS OF MENINGEAL IRRITATION IN DIFFERENT AGE GROUPS

	Signs of meningeal irritation						
	present		*absent*		*doubtful*		
Age group	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Total*
Early infancy	218	41	280	53	31	6	529
Late infancy	257	50	217	43	36	7	510
Early childhood	286	72	102	26	9	2	397
Late childhood	44	83	7	13	2	4	53
Total	805		606		78		1,489

ANALYSIS OF CLINICAL DATA. The frequency of meningeal irritation signs in the different age groups followed a definite pattern. As is evident from Table 2, the older the patients were, the higher was the incidence of signs of meningeal irritation. The difference between the incidence of 53% with no signs of meningeal irritation in the *early infancy group* and the incidence of 13% with no signs of meningeal irritation in the *late childhood group* was

found to be very highly significant ($p<0.01$).

The distribution of the paralytic poliomyelitis cases in the different age groups according to the period of time between the onset of the acute illness and the appearance of muscular weakness or bulbar nuclei involvement did not show a significant difference between the age groups. As is evident from Table 3, about 60% of the patients in each group demonstrated signs of spinal nuclei or nuclei of the medulla involvement, or both, within the first 3 days after the onset of illness, and nearly 90%, before the seventh day.

DESCRIPTION OF LABORATORY DATA. Two major laboratory examinations were considered: the number of white blood cells per c.mm. of cerebrospinal fluid and the amount of protein in 100 ml. of cerebrospinal fluid.

The examination of the number of white blood cells in the cerebrospinal fluid samples obtained on admittance to the ward was performed in 1,306 of the 1,489 cases. The examination of the quantity of protein was performed in 1,240 cases. The failure to perform these tests in all the cases was due to three reasons: moribund condition of patient at time of admittance to the

TABLE 3.—DAY OF ILLNESS WHEN PARALYSES OR SIGNS OF BULBAR NUCLEI INVOLVEMENT, OR BOTH WERE FIRST OBSERVED

	Day of Illness When Paralyses Were Observed									
	1–3		*4–6*		*7–10*		*more than 10*			
Age Group	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*	*Uncertain*	*Total*
Early infancy	225	52	154	35	47	11	11	2	36	473
Late infancy	252	61	113	28	38	9	7	2	60	470
Early childhood	153	58	81	30	26	10	6	2	44	310
Late childhood	18	67	7	26	2	7			2	29
Total	648		355		113		24		142	1,282

TABLE 4.—NUMBER OF WHITE BLOOD CELLS IN CEREBROSPINAL FLUID ON ADMISSION TO WARD

	Number of White Blood Cells per c.mm. of Cerebrospinal Fluid					
	*Normal number**		*Higher than† normal number*			
Age Group	*No.*	*%*	*No.*	*%*	*Total*	*Not known*
Early infancy	80	18	375	82	455	74
Late infancy	61	14	387	86	448	62
Early childhood	48	13	305	87	353	44
Late childhood	2	4	48	96	50	3
Total	191		1,115		1,306	183

*Less than 10 cells per c.mm. of cerebrospinal fluid.
†More than 10 cells per c.mm. of cerebrospinal fluid. The range was between 11 cells and 2,008 cells.

ward, requiring immediate artificial respiration, tracheotomy, or terminating with an exitus lethalis soon after admittance; failure to obtain sufficient quantity of cerebrospinal fluid for performing both tests; and, failure to obtain any fluid, a "dry" or "bloody" tap.

The results of the examinations of the number of white blood cells in the cerebrospinal fluid are summarized in Table 4. The results of the examination of the protein content of the cerebrospinal fluid samples from these patients are summarized in Table 5.

statistically significant ($0.05>p>0.01$).

The protein content in the cerebrospinal fluid samples obtained on admission to the ward was elevated in about half the number of cases in each of the four age groups.

Discussion. The present study was undertaken to establish whether there are significant differences in the clinical picture and cerebrospinal fluid changes in poliomyelitis at different age levels. The group of patients studied represented all the hospitalized pediatric patients with poliomyelitis originating

TABLE 5.—QUANTITY OF PROTEIN IN CEREBROSPINAL FLUID ON ADMISSION TO WARD.

	Quantity of protein per 100 ml. of cerebrospinal fluid					
	*Normal**		*Elevated†*			
Age group	*No.*	*%*	*No.*	*%*	*Total*	*Not known*
Early infancy	192	43	257	57	449	80
Late infancy	207	50	210	50	417	93
Early childhood	174	53	156	47	330	67
Late childhood	18	41	26	59	44	9
Total	591		649		1,240	249

*Less than 30 mg. of protein per 100 ml. of cerebrospinal fluid.
†More than 31 mg. of protein per 100 ml. of cerebrospinal fluid. The range was 31 to 208 mg. of protein per 100 ml. of fluid.

ANALYSIS OF LABORATORY DATA. The incidence of a normal number of white blood cells in the cerebrospinal fluid in the different age groups followed a definite pattern. As is evident from Table 4, the younger the patients were the higher was the number of cases with a normal number of cells (less than 10 per c.mm.). The difference between the incidence of 18% with normal number of white blood cells in the cerebrospinal fluid in the *early infancy group* and the incidence of 4% with normal number of white blood cells in the cerebrospinal fluid in the *late childhood group* was found to be

in northern Israel during the 1950–1956 epidemic. They were observed, treated, and examined by the same medical personnel, thus permitting a uniform recording of clinical and laboratory data.

The four signs assessed and analyzed represent the basis for the diagnosis of poliomyelitis in the acute stage: onset of the disease, signs of meningeal irritation, pleocytosis associated with a normal protein content of the cerebrospinal fluid.

Analysis of the first sign showed that in the majority of this pediatric group of patients the onset was acute and

continuous: The bi-wave pattern was rather rare and noncharacteristic; paralyses or signs of bulbar nuclei involvement, or both, followed in the majority of cases after a short period of temperature and upper respiratory tract inflammation.

The analysis of the second sign, namely the presence of signs of meningeal irritation, such as neck stiffness, bulging of the anterior fontanel, a Kernig's or a Brudzinski's sign, revealed a definite pattern. In the younger group the number of patients who demonstrated signs of meningeal irritation was almost as big as the number of cases in whom no sign of meningeal irritation was elicited on examination. However, the older the patients were, the more frequent was the presence of signs of meningeal irritation.

The analysis of the changes of the cerebrospinal fluid content demonstrated two deviations from the "classic pattern" of the disease. The first deviation was limited predominantly to the *early infancy groups:* about one-fifth of the patients in this group had no pleocytosis. Here as well, the older the patients were the nearer the pattern was to that described in textbooks and texts of reference.

The second deviation was true for the whole group of pediatric patients: in about half the samples of cerebrospinal fluid withdrawn at the onset of the paralytic phase of the disease, the protein content was elevated and higher than the normal of 30 mg. per 100 ml. of fluid. This is in contrast with the pattern in adults, where an elevated number of cells and a normal content of protein is usually observed in the cerebrospinal fluid at this phase of the illness.

The observations on the variability of poliomyelitis at different age levels reported here are evidently of diagnostic importance today. With the universal use of immunizing vaccines, poliomyelitis will become a rare clinical entity, observed in big hospitals' pediatric wards. The differential diagnosis will become harder and more complex. The exact knowledge of the possible and probable variations of the clinical picture and cerebrospinal fluid changes will be a *sine qua non* for an intelligent discussion of differential diagnoses.

Summary. During the first 7 years (1950–1956) of a poliomyelitis epidemic in Israel, 1,489 infants and children with poliomyelitis were treated at Pediatric Department B, Rambam Government Hospital in Haifa.

The analysis of the incidence of the four basic signs of acute poliomyelitis in this pediatric group of patients revealed certain variability of the frequency of these signs at different age levels: a) in the majority of patients under the age of 14 years the onset of the disease was acute and continuous; the bi-wave pattern was rather the exception than the rule; b) the frequency of signs of meningeal irritation in the different age groups followed a definite pattern: the older the patients were, the higher was the incidence of signs of meningeal irritation. The difference of frequencies in the *early infancy group* and in the *late childhood group* was statistically significant; c) the incidence of a normal number of white blood cells in the cerebrospinal fluid during the onset of paralyses was found to be highest in the *early infancy group* and lowest in the *late childhood group;* the difference of these frequencies was also statistically significant; d) in about half the samples of cerebrospinal fluid withdrawn at the onset of the paralytic phase of the disease the protein content was elevated and higher than the normal of 30 mg. per 100 ml. of fluid.

These findings are in contrast with

the pattern in adult patients, where a bi-wave onset, universal presence of signs of meningeal irritation, and an elevated number of white blood cells and a normal protein content are usually observed during the onset of the paralytic phase of the disease.

The clinical importance of the knowledge of the various changes in the clinical picture and cerebrospinal fluid changes in different age groups is discussed and stressed.

SUMMARIO IN INTERLINGUA

Poliomyelitis de Infantia e Pueritia

Durante le prime 7 annos de un epidemia de poliomyelitis in Israel, *i.e.* inter 1950 e 1956, un total de 1.489 infantes e juveniles con poliomyelitis esseva tractate al Departimento Pediatric B del Hospital Governmental Rambam a Haifa.

Le analyse del incidentia del quatro signos fundamental de poliomyelitis acute in iste gruppo pediatric revelava certe differentias secundo le nivello de etate. (1) In le majoritate del patientes de etates de minus que 14 annos le declaration del morbo esseva acute, e le progresso esseva continue. Le configuration bi-undic esseva le exception plus tosto que le regula. (2) Le frequentia del signos de irritation meningee in le varie gruppos de etate se monstrava disponite secundo un ordine specific, *i.e.*, quanto plus avantiate le etate, tanto plus frequente le signos de irritation meningee. Le differentia de iste frequentia inter le gruppo de patientes in le prime infantia e le gruppo de patientes in le pueritia le plus avantiate esseva statisticamente significative. (3) Le frequentia de un normal numeration leucocytic in le liquido cerebrospinal al tempore del declaration del paralyse se monstrava maximal in le gruppo del prime infantia e minimal in le gruppo del pueritia plus matur. Etiam iste differentia esseva statisticamente significative. (4) In circa un medietate del specimens de liquido cerebrospinal obtenite al tempore del declaration del morbo, le nivello de proteina esseva elevate, *i.e.* superior al nivello normal de 30 mg per 100 ml de liquido.

Iste constatationes differe ab le constatationes facite in patientes adulte. In istes, un disveloppamento bi-undic, le presentia de signos de irritation meningee, e un augmento del numeration leucocytic con contento normal de proteina in le liquido cerebrospinal es usualmente observate al tempore del declaration del phase paralytic del morbo.

Es discutite e sublineate le importantia clinic de informationes relative al varie alterationes del aspecto clinic e relative a alterationes del liquido cerebrospinal secundo le varie gruppos de etate.

BIOPLASTIC SUBSTANCE
SIGNIFICANCE OF THE GROUND SUBSTANCE OF TISSUES*

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An apology for the title may be needed, but I wish to emphasize the dynamic characteristics of the amorphous intercellular "stuff" and the important role in physiology and pathology. As a clinician my attention was drawn to this structureless material by the studies of spreading factors by the late Professor Francisco Duran-Reynals of Yale University. He demonstrated that the barrier function of intercellular "stuff" could be altered. An intracutaneous injection of Evans blue dye (T1824) with and without the spreading factor illustrates this function. This factor is the enzyme hyaluronidase derived from bull testes, streptococci and other sources. Testis enzyme acts on both hyaluronate and chondroitin sulfate; bacterial only on hyaluronate. One hour after the intracutaneous injection, the diameter of the spot of dye in the epidermis containing hyaluronidase is larger than the other spot. If the injections are made at different levels of the skin, the visibility of the dye and the rate of spreading are not comparable. Extensive studies of the spread of this nonirritant dye alone and with hyaluronidase (Wydase) in disease have been made and differences in relation to the febrile diseases and hormone changes such as the menstrual cycle are demonstrable, but the impossibility of injecting consistently at the same depth has made quantitative studies unrewarding.

All tissues of the body contain amorphous ground substance which is most prominent in connective tissues. The lubricant function of the synovial fluid has been recognized for centuries. Histologically, the presence of an acidic carbohydrate in tissue may be demonstrated by treating the section with a solution of an iron salt and then staining with a potassium ferrocyanide solution (a so-called reverse Hale stain). Even in glandular organs, such as the kidney and liver, this process produces a green-blue color in the basement membrane and in the epithelial cells. Following the subcutaneous injection of enormous doses of hyaluronidase in the rabbit, a marked increase in hyaluronate-like material (acidic carbohydrate) is apparent both within and around the cells in the kidney and the liver. Hyaluronate appears to be mobilized after injection of the enzyme.

What is hyaluronic acid? The structural formula of the repeating unit comprised of one molecule of N-acetyl glucosamine and one of glucuronic acid is shown in Fig. 1. In combination with a gamma globulin this is the synovial lubricant. Chondroitin sulfate, prevalent in connective tissue (cartilage, around collagen fibers, and others), differs in being a polymer of sulfated N-acetyl galactosamine and glucuronic acid. Structurally it is more rigid. Heparin, connoting anticoagulant action, is present in the mast cells prevalent in many tissues; it is also a sulfated mucopolysaccharide differing from chondroitin sulfate in that sulfate occupies the amino group, a sulfamic derivative,

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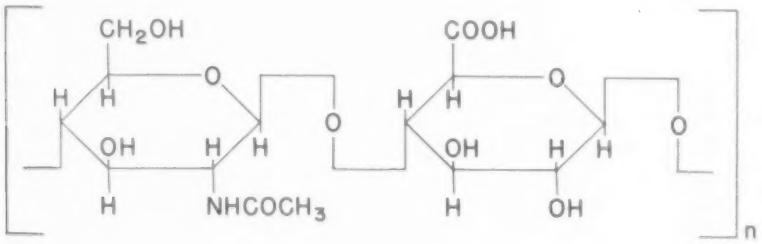
$NHSO_3H$, rather than the alcohol group in the chondroitin sulfate.

A brief version of a tentative classification proposed by Karl Meyer of Columbia University is useful: Mucopolysaccharides are neutral or acid. An example of the former is chitin, the substance of the plant kingdom which is a polymer of N-acetyl-glucosamine; other substances are repeating units of N-acetyl-glucosamine and galactose, namely, the pneumococcus type XIV polysaccharide. The neutral ones tend to have rather firm bonds with protein.



HYALURONIC ACID

Fig. 1

Of the acid mucopolysaccharides hyaluronic acid, as already discussed, is a polymer of repeating units of N-acetyl-glucosamine and glucuronic acid. Heparin is composed of N-sulfamate glucosamine and glucuronic acid. Chondroitin sulfate is N-acetyl-galactosamine, instead of glucosamine, and glucuronic acid. The acid ones tend to bind loosely with protein through polar attraction, hydrogen bridges, Van der Waals forces, and others rather than firmer salt or ester formations, as in the case of sodium chloride or acetic acid for instance, or the attraction of a hydrogen (H^+) of one large molecule with an amino (NH_2^-) portion of another molecule. This seems very complex but it is rather simple considering the actual substances existing in body tissues and fluids. A mucoprotein is a loose combination of a mucopolysaccharide and a protein which is readily split by physicochemical forces and has to do with lubricant action in synovial fluid, for instance. The protein appears to be a gamma globulin in synovial mucoprotein. This mucoprotein withstands shearing force and is a good lubricant; it is thought to be a spiral-shaped molecule. Vitreous mucoprotein of the eye is decomposed by mechanical force but it serves as a supporting transparent gel rather than a lubricant. The nucleus pulposus withstands pressure well until it loses water in old age.

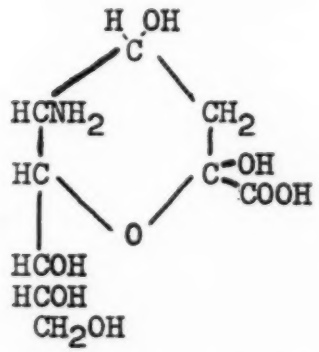
The mucoids are more firmly bound combinations of mucopolysaccharide (L-fucose and amino sugars) and protein, such as the blood group substances and some of the type specific carbohydrates of pneumococci and streptococci.

Glycoproteins are similar protein carbohydrate combinations which, by arbitrary definition, have less than 4% of hexosamine. Lipo-mucoproteins consist of the three components and are important irritants in bacteria. The secretions of mucous membranes and other tissues contain high molecular

size glycoproteins. These contain mucoids and sialomucins. The latter contain sialic acids (derivatives of neuraminic acid) joined with N-acetyl-galactosamine. Neuraminic acid (see Fig. 2) is a labile, complex aminosugar containing hexosamine and pyruvic acid components which is attached to carbohydrates and lipids in erythro-

1) N-acetyl-glucosamine + uridine triphosphate (UTP) $\longrightarrow$ uridine diphospho-acetyl-glucosamine (UDPAG)
2) glucose-1-phosphate + UTP $\rightarrow$ uridine diphosphoglucose (UDPG) $\xrightarrow{\text{DPN}}$ uridine diphosphoglucuronic acid (UDPGA)

NEURAMINIC ACID $C_9H_{17}NO_8$



Gottschalk (1955)

Fig. 2

cytes, mucus, in brain (gangliosides), in urine, and others. Studies of Dr. Paul Gyorgy and his associates at the University of Pennsylvania suggest that the human milk factor is a complex of this type.

Biosynthesis in the mammal of mucopolysaccharides such as hyaluronic acid is not understood. Studies with Group A streptococci and enzymes derived from various microorganisms and tissues have produced precursors of hyaluronic acid from glucose and other simple organic substances. The enzymes required have been demonstrated in human synovial tissue. In condensed form these reactions are:

3) UDPAG + UDPGA + acetyl-glucosamine-1-phosphate $\xrightarrow[Mg^{++}]{ATP}$ hyaluronic acid

To clarify this a little, the structural formula of uridine diphospho-glucose (UDPG) is shown in Fig. 3. Uridine is uracil riboside. In UDPAG, N-acetyl-glucosamine replaces glucose in this formula.

The content of mucopolysaccharides such as hyaluronic acid and the chondroitin sulfates has been determined for some tissues. In embryo skin, 0.5% of polysaccharides are found. Charac-

teristic of young tissues, including a healing wound even in an adult mammal, a ratio of chondroitin sulfate B to hyaluronic acid of 0.2 indicates the predominance of hyaluronic acid. In adult skin, the content decreases to 0.3% and a ratio of 1.25 shows a predominance of chondroitin sulfate. Collagen fibers, being relatively inert metabolically, increase in amount with the passage of the years. The fact that interstitial tissues of the body contain aluronic acid. Remember that collagen increases with age and water decreases in connective tissues.

Hyaluronic acid is formed in the mast cells. Metachromatically staining granules (acid mucopolysaccharide) are seen in the mast cells; heparin is thought to be present in these granules also. The acidic substance changes the color of dyes such as toluidine blue O. Ascorbic acid is required for the synthesis of hyaluronic acid. Although

URIDINE DIPHOSPHOGLUCOSE (UDPG)

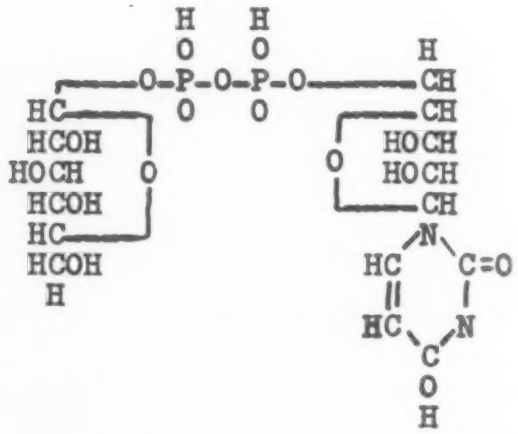


Fig. 3

70% water must be kept in mind. Tendons contain a similar percentage (0.5%) of mucopolysaccharide; in ligamentum nuchae the ratio of chondroitin sulfate to hyaluronic acid is 1.5. In the aorta of the young cow the content is only 0.1% and chondroitin sulfate A is a little less than twice (ratio 1.8) as plentiful as hyaluronic acid. In the aorta of humans in the seventh decade of life, the content of mucopolysaccharide is increased to 0.8% and chondroitin sulfate A is more than four times (ratio 4.3) the hyprocollagen is present in a healing wound, collagen fibers will not form in the absence of hyaluronic acid in the intercellular matrix. In scurvy the incomplete healing of wounds is related to the deficiency of hyaluronic acid and the failure of collagen fiber formation in the damaged tissue. Studies with either the radioisotopes sulfur 35 or carbon 14 show that the half life of hyaluronic acid is very short, only 2 days in the skin. That of chondroitin sulfate is somewhat longer, in the skin 8 days and in cartilage 16

days. Although procollagen has a rapid half life of 2 days, insoluble collagen fibers seem to be permanent.

The effect of certain internal secretions on the ground substance of tissues is of interest and importance. Cortisone and corticotrophin decrease the formation of hyaluronate. These hormones impair capillary permeability, the migration of macrophages, the intracellular digestion of debris and the formation of lymphocytes and plasma cells; however, the degree of polymerization of hyaluronate is increased. Recall the purpura and the thin, transparent skin with striae from rupture of the subcutaneous tissue in Cushing's syndrome. Deoxycorticosterone, on the contrary, increases the formation of both hyaluronic acid and of fibroblasts and collagen. Thyrotrophin causes a replacement of depot fat with a mucinous "stuff" (myxedema) which is composed of hyaluronic acid and water. Thyroid and progesterone decrease formation of hyaluronic acid and the binding of water by intercellular material. Estrogen, androgen and parathyroid hormone increase the formation of hyaluronate. Estrogen increases water binding of connective tissues. Parathyroid decreases the permeability of ground substance.

What are the functions of the amorphous ground substance of tissues? First, the lubricant action has been mentioned and merits further comment. The high concentration of globulin-hyaluronate in the synovial fluid provides a rather ideal lubrication. The molecular size of this mucoprotein is large; it is a random coil of moderate stiffness with entrained solvent (water or rather modified blood plasma) forming a sphere with interconnections between the spheres (molecules). The viscosity of synovial fluid is so-called non-Newtonian, that is, the viscosity varies with the velocity of the motion of adjacent surfaces. At low speeds, viscosity is high and at high speeds viscosity is lower. The joint is well lubricated for either weight-bearing with slow motion of the joint surfaces, where a "thick" oil is needed for boundary lubrication, or for quick movements where a "thin" oil is essential for the rapid motion. The irregular shape of most articulations results in this thinner fluid being forced between the surfaces under pressure during rapid motion, so-called wedge lubrication. Hence, our joints are well lubricated for either slow or fast movement. One of the features of rheumatoid arthritis is the presence of a smaller hyaluronate polymer which has lower viscosity in solution and furthermore does not change viscosity as well with changing rate of motion of the joint surfaces. Trauma, irritation, discomfort and eventually destruction of the articulating surface occurs. Cortisone, either locally or systemically administered, restores the polymer size of the synovial mucoprotein.

Second is the support or cement function. The extraordinary effect of an intravenous injection of crude papaya extract in a young rabbit is recorded by Professor Lewis Thomas of New York University. The ears literally wilt and recover the erect posture in 24 hours. Histological sections show that the amorphous cartilage matrix is dissolved and absorbed. Neither papain nor chymotrypsin alone nor both together have this action and it does not occur in old rabbits. Studies at the National Institutes of Health showed that chondroitin sulfate increases markedly in the blood and slightly in the urine and conclude that the protein-chondroitin complex in cartilage is split. At the 1958 meeting of the Central Society for Clinical Research, Professor William B. Bean, of the University of Iowa, reported a patient with a similar

syndrome: chronic atrophic polychondritis. Hyaluronidase has a similar deleterious effect on the growth of the femur of the chick embryo in tissue culture. The ground substance is required for either bone formation or for collagen formation.

The third function of the amorphous tissue is a barrier to the passage of material such as the spread of bacteria, fluids and chemicals through tissue and between cells and vascular channels. As mentioned already, hyaluronidase enhances the spread of dyes and other dissolved substances in tissues. Initially there was apprehension that the therapeutic use of spreading factor might spread and aggravate infections. This has not occurred perhaps because depolymerization does not progress far enough to liquefy and permit free passage of particulate material. Actually good results in local infections are reported. Considering the comfort and speed of absorption of fluids with Wydase by hypodermoclysis, it is a pity that veins are not saved for more urgent medications. The spreading factor shortens the time of induction and also the duration of anesthesia with water soluble local anesthetics. Experiments of Dr. Joseph Seifter at the Wyeth Institute for Medical Research in Philadelphia show that depolymerized hyaluronate has the same dispersing barrier-permeating action as the enzyme hyaluronidase. Presumably depolymerization *in situ* is the mechanism of spreading action. Because of the concern over nerve gas and the need for an immediately acting antidote, the effect of hyaluronidase on the subcutaneous absorption of atropine, as measured by the salivation induced by pilocarpine, was studied. Protection is almost as rapid as with intravenous injection of atropine sulfate. Unfortunately, for defense purposes hyaluronidase is not sufficiently stable in aqueous solution for prolonged storage.

Fourth, the importance of the amorphous ground substance in the transport of substances is apparent and studies beyond our scope today indicate that mucopolysaccharides are involved in intercellular space as carriers in the sense of an ion exchange resin which combines chemically with substances, entrains them in the folds of their large molecules, adsorbs them by electrical charges, and the like. You are all familiar with the effect of disease and heat on capillary blood flow. The degree of polymerization of the mucopolysaccharides alters the amount of water and electrolytes which can be held. A large polymer can entrain much water without pitting on pressure, a depolymerized ground substance holds less. At pH 6.1, a hydrogen ion concentration compatible with tissue, hyaluronate is neutral, that is, the COOH and NH_2 groups are equal and sodium can pass rapidly, bumping, as it were, the Na^+ off the next molecule. Heat and exercise (motion) change the composition of ground substance gel. Professor Mayerson of Tulane University has studied the disappearance of I_{131}-labeled albumin from the blood following intravenous administration and its appearance in the thoracic duct lymph of the dog. As the radioactivity slowly decreases in the blood it progressively increases in the lymph until the curves meet. This is an evidence of the time required to pass from capillary through ground substance to lymph. The use of drugs with so-called anti-permeability action, such as promethazine, decreases the rate of transfer from blood through ground substance to lymph. The relative roles of capillary, ground substance and lymphatic permeability have not been demonstrated. Conversely, following the intravenous injection of large doses of hyaluronidase (bacterial) in dogs,

Szabo and Magyar in Budapest, Hungary, observed a marked, transient increase in the appearance in lymph of both Evans' blue and I_{131}-labeled serum-albumin. In Brazil, Earp has reported the use of hyaluronidase in the treatment of cerebral edema and Professor Ewen Cameron in Montreal has shown that the blood brain barrier is more permeable following intraarterial or intraspinal injections of hyaluronidase. Drs. Zimmerman and Martins are studying the treatment of acute myocardial infarction with hyaluronidase intravenously (100,000 USP Units every 4 hours). The S–T segment changes, the so-called current of injury in acute myocardial infarction, and the conduction disturbances return to normal in hours rather than in days.

Injection of hyaluronidase into tissue increases the permeability of the intercellular "stuff" and likewise the permeability of adjacent capillaries. Perhaps this is simply a softening of the amorphous, supporting pericapillary substance without any direct action on the capillary *per se*. Intravenous injection in the normal subject of any feasible dose of purified testicular hyaluronidase does not change capillary permeability as measured by studies with Evans' blue, USP. Inhibition of hyaluronidase by the mucopolysaccharides in the blood, nonspecific hyaluronidase inhibitor, was thought to explain this failure. Under some circumstances, however, proteins actually enhance the spreading (depolymerizing) action of hyaluronidase. Studies with radioisotopes of sodium and of potassium by Dr. M. D. Turner at the University of Tennessee have shown a marked increase (62%) in the rate of loss of potassium but not of sodium from the circulating blood into the tissues following the intravenous injection of testicular hyaluronidase. Following injection of histamine intravenously, sodium rather than potassium is lost more rapidly. An alteration of the unidentified substance coating the endothelial cell as a result of the hyaluronidase has been postulated to permit the increased passage of potassium. Since stale testicular hyaluronidase loses this action on potassium but retains its spreading action, the presence of another substance in the partially purified testicular extract is suspected.

The last function I wish to discuss is the dispersing action of mucopolysaccharides. These gels complex with active ions and separate them so that charges do not function and, for example, a concentration of calcium phosphate exists in ground substance which would precipitate in aqueous solution. As you know, enzyme action on the gel has been invoked in the calcification of cartilage. A considerable and variable amount of sodium, water, and other substances are held in the tissues.

Urine specimens from some patients with recurrent renal lithiasis show considerable sediment and turbidity. Following the subcutaneous injection of hyaluronidase the sediment and the turbidity clears for 8 to 24 hours and returns. Dispersing colloids seem inadequate for the amount of solute in the urine. In the rabbit, an increase in urinary glucosamine occurs after such an injection of Wydase. Recalling the increased Hale stain in the kidney mentioned already, it is inferred that mucopolysaccharide is mobilized and excreted. This method of increasing dispersing substance in the urine of patients with recurrent renal lithiasis has not proven sufficiently effective particularly in the presence of pyuria. Other methods of study of urine have shown inadequate dispersing colloids in such patients. Aspirin to increase glucuronides in the urine is also feeble therapy. However, the clinical trials

with hyaluronidase subcutaneously encourage research to find an effective protective colloid to deal with this and perhaps other problems of abnormal calcifications.

I have brought you little of practical therapeutic application, but I hope this brief discussion of our growing appreciation of the nature of intercellular substance and its role as a lubricant for joints and tendons, in support, as a barrier, in active transport and as a physiological dispersing agent will stimulate your further curiosity.

REFERENCES

In a general lecture a complete list of references does not seem pertinent. For the curious a list of recent symposia or reviews follows:

1. **Asboe-Hansen, G.:** Physiol. Rev., **38**, 446, 1958.
2. Idem (Ed.): Connective Tissue in Health and Disease. Copenhagen: E. Munksgaard, p. 321, 1954.
3. **Blumberg, B. S.:** Bull. Rheum. Dis., **9**, 169, 1958.
4. **Bryant, J. A, Leder, I. G.,** and **Stetten, DeW., Jr.:** Arch. Biochem. & Biophysics, **76**, 122, 1958.
5. **Butt, A. J.** (Ed.): Etiologic Factors in Renal Lithiasis. Springfield, Ill.: Charles C Thomas, p. 401, 1956.
6. **Castor, C. W.:** Bull. Rheum. Dis., **9**, 177, 1959.
7. **Jordao, A.,** and **Sa Earp, F. A. de:** Bol. d. Centro d. Estudos do Hospital dos Servidores do Estado, Rio de Janeiro, N. 5–6, (May–June), 1955.
8. **Meyer, K.** (Chairman): Fed. Proc., **17**, 1074, 1958.
9. **Ragan, C.** (Ed.): Connective Tissues. New York: Josiah Macy, Jr. Foundation, 1954.
10. **Slack, H. G. B.:** Am. J. Med., **26**, 113, 1959.
11. **Springer, G. F.** (Ed.): Polysaccharides in Biology. New York: Josiah Macy, Jr. Foundation, 1955.
12. **Szabo, G.,** and **Magyar, S.:** Nature, **182**, 377, 1958.
13. **Wolstenholme, G. E. W.,** and **O'Connor, M.** (Eds.): Chemistry and Biology of Mucopolysaccharides. Boston: Little, Brown & Co., p. 323, 1958.

(Interlingua on page 684)

COMPLICATIONS OF INFECTIOUS MONONUCLEOSIS

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Pfeiffer[47], in 1889, first described infectious mononucleosis as a clinical entity in his treatise on "Drusenfieber," delineating it as a benign infection of children. Since that description, much has been added to our descriptive knowledge of infectious mononucleosis, but the underlying cause remains obscure.

Refinement of certain hematological and serological techniques has made detection more certain, but has also made it evident that, in certain instances, this disease may produce marked derangement in normal physiology and pathology, and progress to a fatal ending.

It is not the purpose of this paper to dwell on the well-recognized picture of the uncomplicated case of infectious mononucleosis, but instead to focus attention on the kaleidoscope of complications that may occur as a result of this disease process. The following case summaries are examples of five of these complications seen at this hospital. They are presented both because of the severity of manifestations in the several cases and to cite the unusual complication of a winged scapula resulting from infectious mononucleosis which has not previously been reported.

Case Reports. CASE 1. R.D.W. This 14-year-old, white boy was admitted on July 24, 1958, complaining of weakness, lethargy, anorexia, pallor and jaundice. He had noted gradual onset of weakness, lethargy and anorexia 3 weeks prior to admission, concurrently noting increasing pallor. Two weeks prior to admission, he observed dark urine. These symptoms and signs persisted until 5 days prior to admission, at which time he was found to be jaundiced. He was admitted to a local hospital where hemoglobin of 8.5 gm., leukocytosis of 23,000 and a total bilirubin of 5.3 mg. per 100 ml. were noted. He became quite confused, very weak on standing and fainted twice on attempting to walk. Temperature at this time was approximately 102°. He was then transferred to this hospital.

Past medical history, family history and system review were essentially negative. Physical examination revealed blood pressure 118/55, pulse 112, temperature 100.2°. He was a well-developed obese boy who appeared acutely ill. Examination of the head and neck showed small posterior cervical nodes on the left. Head, eyes, ears nose and throat showed only scleral icterus. Chest examination was negative to percussion and auscultation. A Grade II apical systolic murmur, transmitted to the left sternal border, was present. The liver was percussed 2 cm. below the right costal margin and was tender. Spleen and kidneys were not felt. The genitalia were normal. Rectal examination was negative and the remainder of the physical examination was normal.

Laboratory and Roentgenographic Examination: Urinalyses: three urinalyses were negative for bile and sugar, one showing 1+

albumin. White count on admission was 16,650; hemoglobin 24% or 3.7 gm.; hematocrit 14.5; polymorphonuclear leukocytes 55%, lymphocytes 32%, monocytes 6%, metamyelocytes 4%, myelocytes 3%. There were 8% atypical lymphocytes. There were 6.4% reticulocytes. Four days after admission, the white count was between 4,000 and 6,000, the differential showing increased lymphocytosis with a high of 62%, 6% of which were atypical. Reticulocytes reached a high of 32.5% the day prior to dismissal, August 3, 1958. Blood urea nitrogen was 15 mg. per 100 ml., creatinine 1.4 mg. per 100 ml., CO_2 23.9, sodium 138, potassium 5 mEq./L. Hepatogram revealed a total bilirubin of 2.9 mg. per 100 ml. with direct 0.9 mg. per 100 ml. Alkaline phosphatase was 3.4 mM. units; cephalin flocculation 4+; thymol turbidity 28 units; serum albumin 3.91 gm.%; serum globulin 3.38 gm.%; total cholesterol 120 mg. per 100 ml. with 62% esters; and serum iron 371 μg. per 100 ml. The Coombs' test was negative. Fecal urobilinogen was 1872 mg. in 72 hours. Blood indices were normal; platelets were 306,000. Three days later, cephalin flocculation was 4+; total bilirubin 3.2 mg. per 100 ml., direct 0.8 mg. per 100 ml.; thymol turbidity 28 units. Three days prior to discharge, August 1, 1958, serum iron was 130 μg. per 100 ml.; BSP 5% retention; thymol turbidity 21 units; bilirubin: total 2.2 mg. per 100 ml., direct 0.3 mg. per 100 ml.; transaminase 20 units; 2-hour urinary urobilinogen reached a high of 31.5 mg. per total volume of 500 ml. An LE preparation was negative. Blood ammonia was 100 μg. per 100 ml. One day after admission, the heterophil titer was positive in dilutions of 1:896 and there was no absorption on guinea pig kidney. Febrile agglutinins were negative. The heterophil titer remained the same on two additional examinations. Electrocardiogram was normal. The chest film and pyelogram were within normal limits.

Hospital Course: The patient rapidly improved. The temperature on admission was 102°, returning to normal 2 days after admission. He was afebrile during the remainder of his hospitalization. Medication included cortisone in doses of 100 mg. daily for the first 5 days, 75 mg. on the sixth day, 50 mg. on the seventh and eighth days, and he was dismissed on 25 mg. in the morning and 25 mg. in the evening. Hemoglobin on discharge was 6.7 gm., and 2 months later was 13.5 gm. (see Fig. 1).

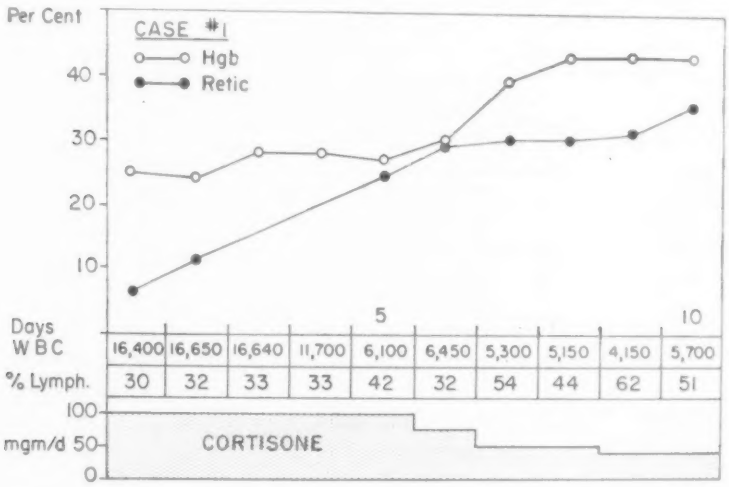

Fig. 1.—Hematologic data, Case 1.

CASE 2. R.W., a 13-year-old white boy admitted on May 18, 1953, with the chief complaint of abdominal pain and fever. He was well until approximately 2 weeks prior to admission, when he noted the onset of periumbilical and right upper quadrant pain and low-grade fever. He was placed in a local hospital and blood counts initially showed a relative leukopenia and lymphocytosis, which then changed to a leukocytosis with marked lymphocytosis. The pain and

temperature persisted and the patient was admitted here with the possible diagnosis of leukemia.

Physical Examination: Temperature 99.2°, blood pressure 120/80, pulse 90, respirations 16. The patient was a well-developed, obese boy. There was no jaundice nor petechiae. Examination of the head and neck was normal, as were the eyes, ears, nose and throat. The chest was normal to percussion and auscultation. Heart showed a normal sinus rhythm without murmur or thrills; P_2 was equal to A_2. The liver was palpable two finger breadths below the right costal margin and tender, and the spleen was not felt. The remainder of the physical examination was normal.

Laboratory Examination: Admission urinalysis showed a specific gravity of 1.018; albumin and sugar were negative; there were 1 to 2 pus cells per hpf. Red count was 4,250,000; hemoglobin was 85% or 12.8 gm.; white count 13,800, polymorphonuclear leukocytes 6%, lymphocytes 90%, monocytes 4%. VDRL nonreactive. Hepatogram: Serum bilirubin: total 0.4 mg. per 100 ml., direct 0.2 mg. per ml.; serum albumin 4.34 gm.%; serum globulin 2.66 gm.%; alkaline phosphatase 2.7 mM. units; thymol turbidity 15; cephalin flocculation 4+; BSP 17%; cholesterol, 184 mg. per 100 ml. total and 67% cholesterol esters. Heterophil was positive in dilutions of 1:896. On May 19, 1953, the white count was 10,100 with 92% lymphocytes, polymorphonuclear leukocytes 4%, monocytes 3%, basophils 1%; 53% of the lymphocytes were considered to be atypical; platelets were 280,000; hemoglobin was 75% or 11.6 gm. The bone marrow was essentially normal.

Hospital Course: The patient was afebrile throughout the course of his hospitalization. On the day after admission, the right upper quadrant pain had diminished. At discharge, he was asymptomatic. He was placed on moderate bed rest and no other medication.

CASE 3. W.S. This 18-year-old, white boy was admitted on November 1, 1956 in a semistuporous state. On October 19, 1956 the patient had noted fever, headache, nausea and vomiting, and right quadrant pain, continuing in severity. He was admitted to a local hospital on October 26, 1956, five days prior to admission here. At that time he was jaundiced, with direct serum bilirubin 2.2 mg. per 100 ml., indirect 2.95 mg. per 100 ml. Admission complete blood count showed 29% polymorphonuclear leukocytes, 64% lymphocytes and 7% monocytes. The clinical course gradually worsened and the patient became stuporous on October 29, 1956. He had difficulty in talking, swallowing and controlling secretions; however, these signs improved slightly to the point where, on admission here, he was able to swallow. Concurrent with the onset of stupor, he had developed a flaccid paralysis of his legs. Spinal fluid had revealed 176 leukocytes with 70% lymphocytes.

Past medical history, family history and system review were noncontributory. Physical Examination: Blood pressure 120/60, pulse 92, respirations 16, temperature 101° (rectal). The patient was a well-developed, well-nourished, white male with slurred speech, lying quietly in bed. Examination of the head and neck showed only moderately enlarged posterior cervical nodes. Examination of the eyes demonstrated a lack of accommodation with a sixth cranial nerve palsy. There was an absent gag reflex and the tongue deviated slightly to the right. The only abnormality found on examination of the chest and heart was occasional basilar rales. The liver was palpable two finger breadths below the right costal margin. The spleen was palpable two fingerbreadths below the left costal margin. Neurological examination revealed slurred speech with bilateral sixth cranial nerve weakness. Both lower extremities were paralyzed; however, the deep tendon reflexes were present. Abdominal and cremasteric reflexes were absent, and a sensory loss at the level of T–3 on the right and T–5 on the left was present. There was no nuchal rigidity.

Laboratory Examination: Urinalysis showed a specific gravity of 1.028; albumin, sugar and microscopic examinations were negative. During the course of the hospitalization, he developed a urinary tract infection, and white blood cells and bacteria were demonstrated in the urine. Urine culture revealed *Pseudomonas aeruginosa*, resistant to most antibiotics. Complete blood counts were done on 15 occasions. Admission white count was 12,850; hemoglobin was 15 gm.; polymorphonuclear leukocytes 41%, lymphocytes 56%, basophils 1%, monocytes 2%. Several atypical lymphocytes were noted. Serum electrolytes were normal. The initial spinal fluid examination revealed 3 leukocytes, colloidal gold curve normal, sugar 55 mg. per 100 ml., protein 39 mg. per 100 ml.; the second examination (5 days later) revealed 2 leukocytes, sugar 56 mg. per 100 ml., protein 82 mg. per 100 ml. Febrile agglutinins were negative. On admission the heterophil antibody titer was positive in dilutions of 1:448; repeat heterophils were positive in dilutions of 1:224 and

1:224 with guinea pig kidney absorption. The serum bilirubin was 1.2 mg. per 100 ml. The alkaline phosphatase was 4.5 mM. units. Bromsulphalein retention was 9%. Cephalin flocculation was 3+. The thymol turbidity was 14 units; serum albumin was 2.05 gm.%; and the total cholesterol was 152 mg. per 100 ml. with 68% esters. The cephalin cholesterol was 3+ and the BSP retention was 4% ten days later.

Hospital Course: The patient was acutely ill on admission, but rapidly improved with return of muscle tone in the lower extremities, improvement in the ocular palsies, and gradual loss of the sensory defect. He developed a urinary tract infection with incontinence, but without residual urine, and was found to have an uninhibited neurogenic bladder by cystometrograms. He was discharged on December 2, 1956, and was walking alone; however, he continued to have slurring speech and diplopia. He also had slight sensory defect and motor weakness in both legs, in addition to the neurogenic bladder. Discharge diagnosis was infectious mononucleosis with hepatitis and encephalomyelitis, and uninhibited neurogenic bladder.

CASE 4. B.G. This 26-year-old, white woman was admitted on November 19, 1952, complaining of sore throat and fever. Approximately 2 weeks prior to admission she had developed a sore throat, fever and malaise. One week prior to admission, she had noted the onset of swelling of the lymph nodes in her neck and, following an episode of vomiting, coughing and increasing malaise, was admitted to the hospital. Two weeks prior to admission, she noticed weakness in her right arm, limiting movement of her arm over her head. Concurrently, she stated her right scapula felt as if it "was dislocated."

Physical Examination: Blood pressure 126/60, pulse 96, respirations 16, temperature 101.2°. She was a thin, white girl appearing acutely ill. Examination of the head and neck revealed anterior cervical adenopathy. There was marked injection of the pharynx with tonsillar exudate and plaques. Examination of the chest and heart was negative except for an elevated and prominent right scapula. The liver was palpable two finger breadths below the right costal margin and the spleen was palpable two finger breadths below the left costal margin. The remainder of the physical examination was within normal limits.

Laboratory Examination: Admission urinalysis revealed albuminuria and glycosuria with numerous pus cells. Repeat urinalysis 2 days later was within normal limits. The white count was 21,600 with 24% polymorphonuclear leukocytes, 74% lymphocytes and 2% eosinophils. Hemoglobin was 11.8 gm.%. On December 10, 1952 the white count was 9,650 with 61% polymorphonuclear leukocytes, 33% lymphocytes, 3% eosinophils and 3% monocytes. Serology was negative. The nonprotein nitrogen was 33 mg. per 100 ml., glucose 95 mg. per 100 ml., sodium 139 mEq. per L., potassium 4.6 mEq. per L. and chlorides 102 mEq. per L. Glucose tolerance test was normal. Heterophil antibody titer was positive in dilutions of 1:8192 on admission. The direct bilirubin was 0.2 mg. per 100 ml. with a total of 0.6 mg. per 100 ml., alkaline phosphatase was 12.2 mM. units, Bromsulphalein retention was 5% in 45 minutes, thymol turbidity was 24 units and cephalin flocculation was 4+. The serum albumin was 4.0 gm.%, and the serum globulin 3.0 gm.%.

Hospital Course: She was initially febrile with a temperature of 101.2°, which fell rapidly to normal values with no further elevation. She gradually improved on therapy including a low-fat, high-carbohydrate, high-protein diet, penicillin, aureomycin and vitamin B_{12}. On discharge the hepatomegaly and splenomegaly were diminished; however, the winging of the right scapula persisted and was present on further examination after dismissal, and was present on examination one year later (see Fig. 2).

CASE 5. J.S., a 16-year-old, white girl, was admitted with the chief complaint of "fever and weakness" on October 30, 1958.

The patient was well until 5 days before admission and had played in the high-school band on the day prior to her illness, when she became chilled and, the following day, awoke with a temperature of 101.6°. That evening her temperature rose to 104° and she was admitted to a local hospital. Physical examination and neurological findings at that time were essentially negative. On October 28, three days after the onset of her illness, she vomited and, on the next day, became lethargic with stiffness of the neck, headache, divergence of the eyes, diplopia and weakness of the lower extremities. At this time, deep tendon reflexes were diminished on the right. Lumbar puncture revealed an opening pressure of 170 mm. of water with a white cell count of 78, most of which were lymphocytes. Cerebrospinal fluid protein was 66 mg. per 100 ml. The white cell count was 14,000, with 49% lymphocytes, 36% polymorphonuclear leukocytes and 15% monocytes. Agglutinations for typhoid, paratyphoid, brucella were neg-

tive. Heterophil was positive in dilutions of 1:4. She developed sighing respirations. The temperature rose to 105°. She developed weakness of both upper and lower extremities and was subsequently transferred to this hospital, 5 days after the onset of her illness.

Past medical history, family history and systems review were essentially negative.

Physical Examination: Blood pressure 110/80, pulse 80, temperature 105° (rectal), respirations 24. She appeared acutely ill, and was very lethargic. The pupils were small but the funduscopic examination was normal. Extraocular movements were also normal. Posterior cervical nodes and slight nuchal rigidity were present. The respirations were diaphragmatic in nature, and coarse rhonchi were heard throughout both lung fields. Cardiac examination was not remarkable. Neurological examination demonstrated an active gag reflex, but she was unable to swallow. Flaccid paralysis of both lower extremities and marked weakness in the upper extremities, and bilateral facial weakness were present. Deep tendon reflexes were absent. There was a plantar response bilaterally. Sensory examination revealed impaired pain sensation, although light touch sensation was present.

Laboratory Examination: Urinalysis negative. The white count was 12,100 with 59% polymorphonuclear leukocytes, 37% lymphocytes, 4% monocytes with 13% atypical lymphocytes; hemoglobin 12.2 gm.; hematocrit 35%; blood urea nitrogen 12 mg. per 100 ml.; CO_2 24.4 mEq. per L.; sodium 131 mEq. per L.; potassium 3.8 mEq. per L.; chlorides 95 mEq. per L. Examination of the cerebrospinal fluid revealed normal pressure; there were 165 leukocytes with 80% lymphocytes and 75 red cells; spinal fluid sugar was 58; total protein 97 mg. per 100 ml. Heterophil antibody titer was now positive in a dilution of 1:896. Agglutinations for typhoid, paratyphoid and brucella were negative. The alkaline phosphatase was 1.6 mM. units, direct bilirubin 0.3 mg. per 100 ml .and total 0.8 mg. per 100 ml., thymol turbidity 9 units, serum albumin 2.76 gm.%, serum globulin 1.93 gm.% and the cephalin flocculation was 3+.

Hospital Course: Shortly after admission, a tracheotomy was performed and she was started on penicillin. On the day following admission, spontaneous respirations ceased and the patient was placed in a Drinker respirator. The temperature remained between 104 and 105°. On November 1, 1958, corti-

Fig. 2.—Permanent winged scapula, Case 4.

sone was started. In 24 hours, the temperature had fallen to levels of 95.6 to 98.6° F. and remained below 99° F. until her death. Repeat heterophil studies were done 4 days after admission and were positive in dilutions of 1:448 with complete absorption on beef red cell and no absorption on guinea pig kidney. The patient remained in a stupor. She was maintained on intravenous fluids and was given constant nursing care in the respirator. Twenty-one days after admission and 26 days after the onset of her illness, she became cyanotic, pulse and blood pressure were unobtainable, and she was pronounced dead.

Postmortem Findings: Grossly, the entire brain was greatly softened and friable; dura was adherent to the cerebral hemisphere and the entire brain appeared necrotic, and in most areas both gray and white matter were crumbly or jelly-like. Histological examination showed severe degenerative changes throughout all sections. In the deeper portion of the brain these consisted of edema, friability and disintegration of the glial network, with slight to moderate loss of staining of the myelin sheaths and of the nerve fibers. No inflammatory exudate was present in these deeper areas. The glial nuclei were pyknotic or appeared normal. The neurons of the pons, dentate nuclei and medulla were present but showed loss or peripheralization of Nissl's substance or eosinophilia of the cytoplasm with nuclear pallor (see Fig. 3). Near the surface of the cerebrum, medulla and cerebellum there was frank necrosis with complete loss of structure and invasion from the leptomeninges of neutrophils, many of which were disintegrating, and an occasional gitter cell. The leptomeninges were adherent and showed fibrovascular proliferation, focal necrosis and infiltration by neutrophils and histiocytes (Fig. 4).

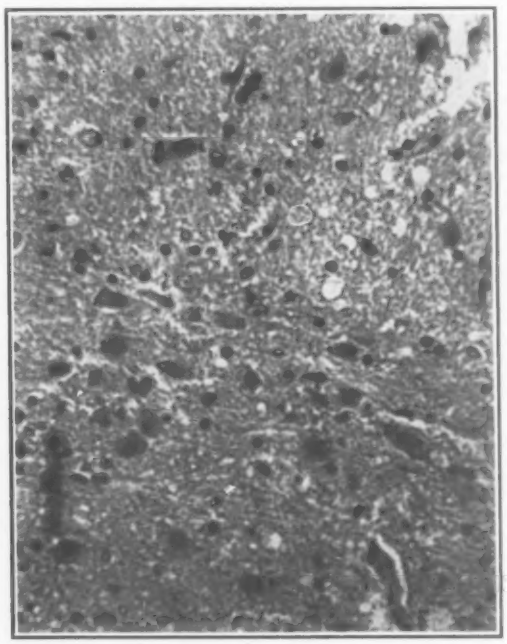

Fig. 3.—Case No. 5. Striate substance of pons. Edema and disarrangement. Degenerative changes in neurons.

Discussion. It would appear justifiable to present a brief review of the literature regarding the complications of this disease which, in spite of the advances made in its detection, continues to baffle as to etiology and pathogenesis.

NEUROLOGIC COMPLICATIONS. The first case of infectious mononucleosis with neurological complications was described in 1931 by Epstein and Dameshek[20], who presented a case of infectious mononucleosis with meningoencephalitis and complete recovery in 38 days. Custer and Smith[16] in 1948 reviewed necropsies from 9 patients with infectious mononucleosis and found the central nervous systems showed congestion of the meninges with moderate numbers of mononuclear cells and occasional small perivascular hemorrhages within the brain substance, as well as mild ganglion cell degeneration. The incidence of neurological complications has been reported to be 1% or less (Bernstein and Wolfe[5], Pew[46]); however, the mortality may be 15 to 40% in these cases (Lawrence[37]). Electroencephalograms have been used to detect more subtle changes (Bercel[3]). This is perhaps useful as another parameter in detecting early neurological involvement. Meningeal irritation, headache and visual abnormalities are usually the first clinical signs of neurological involvement. Infectious mononucleosis may manifest itself as encephalitis, peripheral neuritis, meningitis, ataxia, diplopia, coma, hyperesthesia, nystagmus, papilledema and mental confusion. The signs of neurological involvement may precede the more classic manifestations of infectious mononucleosis by several days, and these are frequently minimal or absent. Cortisone has been reported to be of benefit (Frenkel *et al.*[23]) in these complications and, as seen in Case 5, its addition was followed by a drop in temperature; however, little else of benefit was

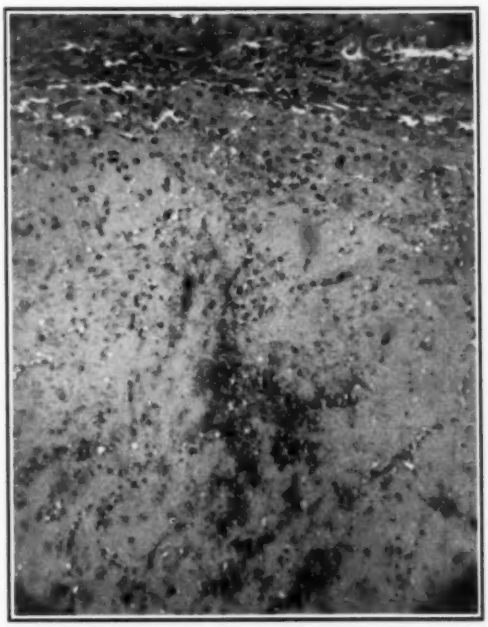

Fig. 4.—Case No. 5. Cerebral cortex (leptomeninges at top). Necrosis with disintegration and inflammatory infiltrated.

seen to occur. Bernstein and Wolfe[5] in 1950 reviewed the literature and classified the neurological complications as follows: Serous meningitis (4 cases), encephalitis (4 cases), meningoencephalitis (4 cases), meningitis (10 cases), meningitis or meningoencephalitis with acute polyneuritis (7 cases) and peripheral neuropthy (6 cases).

The clinical picture in Case 5 of disorientation, weakness, slurred speech, lethargy, coma, absent deep tenden reflexes, pathological reflexes and signs of cranial nerve palsies, in addition to the findings at postmortem examination, would indicate that this was meningoencephalitis. Case 3 demonstrates an example of encephalitis and transverse myelitis complicating infectious mononucleosis; however, there was almost complete clearing of the neurological signs after one month. Case 4 illustrates a winged scapula following infectious mononucleosis. This represents an instance of peripheral neuropathy with irreversible neurological deficit which persisted after the clinical signs and symptoms of infectious mononucleosis had disappeared.

Since the report by Bernstein and Wolfe, there have been additional cases of infectious mononucleosis with neurological involvement reported (Bercel[3], Betts, Siekert and Clark[6], Canter and Schillhammer[11], Coogan, Martinson and Matthews[14], Dixon[18], Frenkel *et al.*[23], Green[25], Hollister, Houck and Dunlap[29], Klein[35], Riske-Nielsen and Mogensen[50], Smith[56]. The first reported case of infectious mononucleosis complicated by the Guillain-Barré syndrome was in 1945 (Coogan[14]) in which is described the typical bilateral ascending paralysis and albumino-cytologic dissociation in the spinal fluid. This is now recognized as one of the complications of infectious mononucleosis. Infectious mononucleosis has been reported to have caused over 20 cases. Death, when it occurs, is due to a respiratory paralysis. Spinal fluids generally have been reported as negative for the heterophil antibody; however, in 1948 (Silverstein, Bernstein and Stern[55]) the heterophil antibodies were found in the cerebrospinal fluid of 6 patients with infectious mononucleosis out of 654 routine spinal fluids examined. Atypical lymphocytes have been reported in the spinal fluid in one case (Hollister, Houck and Dunlap[29]). These factors may be of further value in the diagnosis. It is obvious from the foregoing that the neurological manifestations are predicated by the site of maximum cellular infiltration and practically any symptom may be produced, from transitory ocular palsies to death. While complete recovery is the rule, permanent neurological deficit or death may occur, as demonstrated in the cases reported above.

OCULAR MANIFESTATIONS. No necropsy reports are as yet available regarding optic involvement in infectious mononucleosis; however, 3 cases have been reported demonstrating papilledema without neurological involvement in association with infectious mononucleosis (Asworth and Motto[1], Blausten and Caccavo[7], Karpe and Wising[33]). In a review of the ocular manifestations of infectious mononucleosis, Tanner in 1954[59] divided them into two groups: 1) Those possibly due to direct involvement of the eye and its adnexa by the characteristic pathological lesion in infectious mononucleosis (examples being conjunctivitis, periorbital and eyelid edema, uveitis, optic neuritis, papilledema, and retinal hemorrhage [Stevens[58]]); and 2) those affecting vision as a result of a lesion not in the eye proper (examples being extraocular muscle palsies, ptosis, nystagmus, hemi-

anopsia and scotomata). In this same review, the most common eye complaints in infectious mononucleosis were found to be pain in or behind the eyes, edema of the conjunctiva and redness of the conjunctiva.

PULMONARY COMPLICATIONS. In 1946, Wechsler[65] reviewed findings in an epidemic of infectious mononucleosis and reported pulmonary complaints in 5%. These symptoms were cough, wheezing, sputum and rales. Roentgenographic evidence of pulmonary involvement was present in 2.7%, consisting of a picture indistinguishable from that of primary atypical pneumonia. They found no evidence of mediastinal lymph node involvement. Custer and Smith[16], in necropsy specimens, found interstitial pneumonitis, indistinguishable from the picture produced by primary atypical pneumonia, influenza or rheumatic pneumonitis. Vander, in 1954, reported the first case of pleural effusion in infectious mononucleosis[62], and Briggs, Bellomo and Zauner[9] in 1956 reported a case of hemorrhagic pleural effusion complicating infectious mononucleosis.

RENAL COMPLICATIONS. In necropsy specimens, in a review previously cited by Custer and Smith[16], the kidneys showed infiltration of lymphocytes in the interstices of the cortex and the periphery of the small blood vessels; however, there was no evidence of alteration in the nephrons. Tidy and Daniel[61], in 1933, reported an epidemic and found hematuria to be a presenting manifestation in 6% of the cases. This, in all probability, represents an interstitial nephritis. Microscopic findings in the urine frequently show albuminuria, pyuria and occasional hyalin casts, but evidence of permanent impairment of renal function as yet has not been presented (Bernstein[4], Krasnow[36], Stevens[58]).

CUTANEOUS MANIFESTATIONS. In an analysis of 210 sporadic cases (Stevens[58]) 7.6% were found to have cutaneous manifestations. These would appear to be practically unlimited in nature and have been described as being maculopapular, vesicular, herpetiform, erythematous or scarlatiniform types of rashes. Skin eruptions appear generally during the first phase of the disease and fade within a few days. The sites of predilection are the trunk and arms, occasionally the face and forearm, and rarely the hands, thighs, legs or feet. In 1954, a case of genital ulcer with infectious mononucleosis was reported (Kallos[32]). This ulcer cleared as the infectious process subsided, but initially presented a problem in differential diagnosis. Also of interest is the enanthem of infectious mononucleosis which is typically described as multiple pin-point petechiae on the palate. These generally appear 3 days to 2 weeks following the onset of symptoms and last approximately 3 to 5 days (Shiver, Berg and Frenkel[53]). It is felt that multiple palatine petechiae in absence of petechiae elsewhere represent a valuable aid in diagnosis.

ABDOMINAL COMPLICATIONS. Melville states that the most common single cause of death in infectious mononucleosis is spontaneous rupture of the spleen[41]. Smith and Custer[16] found infectious mononucleosis to be the cause of spontaneous rupture of the spleen in 7 of 44 cases, and was second only to malaria as the cause of this complication. Since then, there have been further reports of splenic rupture, both spontaneous and traumatic, in association with infectious mononucleosis (Connell and Clifton[13], Melville[41] Wagman[63]). The incidence of splenomegaly in infectious mononucleosis has been estimated to be 40 to 80%. In those cases where splenic rupture was a complication, approximately 40% were

spontaneous ruptures, with the mortality approximating 30% (Connell and Clifton[13]). This complication is rare before the end of the second week, since this period is required for the pathologic changes to occur; that is, infiltration of the capsule with lymphocytes and monocytes, increase in bulk of the splenic pulp and blurring of the normal architectural pattern (Shecket[52], Wisner[66]). The end result of these changes is a rapid enlargement of the organ with stretching of the capsule and subsequent possible rupture. It should be emphasized that very minor trauma such as defecating, vomiting, getting out of bed, or palpation may be sufficient to produce rupture. The signs to be expected are those of peritoneal irritation with upper abdominal pain, bleeding and shock; however, evidence of massive bleeding and shock may be delayed for several days due to formation of a subcapsular hemorrhage and slow leakage of blood. If these signs are awaited by the physician, the chances for the patient's recovery may be seriously impaired. Surgery in these instances may be lifesaving. In addition to splenic rupture, patients may present with abdominal pain (Smith[56]), and this may simulate an acute abdomen. In some instances, the etiology of the abdominal pain most likely is lymph node engorgement and hyperplasia; however, there have been case reports of infectious mononucleosis associated with pancreatitis (Mhyre[42]) and with pain over McBurney's point, with considerable difficulty in differentiating from acute appendicitis (Gilbert[24]). In these cases, the differential of the initial white blood cell count with its demonstration of abnormal lymphocytes is of paramount importance in arriving at the correct diagnosis and perhaps sparing the patient a needless operation.

HEPATIC COMPLICATIONS. Case 2 was presented not because of any extraordinary complications contained therein but as a reminder that a degree of liver involvement may be expected to accompany any uncomplicated cases of infectious mononucleosis. Liver involvement in infectious mononucleosis is somewhat difficult to assess; however, the available information would seem to indicate an incidence of between 85 to 100%. It is now fairly well documented that the hepatic lesion in infectious mononucleosis is a form of hepatitis which, in most instances, is clinically and microscopically indistinguishable from that produced by viral hepatitis (Burke and Davis[10], Krasnow[36], Rennie and Wroblewski[49], Wolfe and Fine[67]). In 1956, Nelson and Darragh[44] studied 22 cases of infectious mononucleosis and found evidence of hepatic involvement, as measured by liver function tests, in all cases. Liver biopsies of these same patients showed focal hepatic necrosis in 9, or 40%; portal exudate consisting of mononuclear cells in 20 of the cases, or 90%; and invasion of the sinusoids by mononuclear cells in 20 of the cases, or 90%. Biopsy evidence of hepatitis was not present after the fifth week. In a study in 1946 (Cohn and Lidman[12]), liver function studies showed evidence of hepatic involvement in all 15 cases studied. Necropsy reports (Burke and Davis[10], Custer and Smith[16]) have shown periportal hepatitis and hepatic necrosis with infiltration of mononuclear cells in the periportal and sinusoidal areas, giving a picture indistinguishable from viral hepatitis. Jaundice as a complication was first reported by Mackey and Wakefield in 1926[39], its incidence is now reported to be approximately 5% (Wormer, Martin and Wollaegen[68]) and, when present, represents further evidence of hepato-cellular damage. While it is generally assumed that recovery is

complete from this form of hepatitis, there have been case reports raising the question of chronic liver disease resulting from infectious mononucleosis (Jordan and Allbright[31]). Liebowitz and Brody[38], in 1950, reported a case of cirrhosis 3 years after an episode of infectious mononucleosis and discussed the possibility of this complication as another sequelae. There was, however, a history of alcoholism and poor nutrition also associated in the clinical picture of this patient, and these factors may have been of prime importance in the production of the resultant cirrhosis. In 1952, Marshall and Millingen[39] reported a fatal case of infectious mononucleosis with acute hepatic necrosis. The postmortem examination showed perilobular fibrosis, cellular infiltration in the periportal areas and areas of hepatic necrosis.

HEMATOLOGICAL COMPLICATIONS. Case 1 was presented to demonstrate the severity of a hemolytic anemia which may accompany infectious mononucleosis. The hemoglobin level was 3.7 gm. on admission. Downey and McKinley[19], in 1923, stated that the absence of anemia in infectious mononucleosis was an important sign when attempting to differentiate this condition from other hematological conditions producing abnormal blood pictures. However, this statement has subsequently been shown to be incorrect. In 1943, Dameshek reported the first case of hemolytic anemia in association with infectious mononucleosis[17]. The clinical picture was that of a patient with infectious mononucleosis who had been on sulfadiazine, with a hemolytic process occurring 11 days after the onset of the disease. A circulating autoagglutinin was detected, showing different properties from the heterophil antibody, which disappeared as the titer of the heterophil antibody dropped. At that time, Dameshek felt that the agglutinin was more likely related to the infectious process than to the medication. In 1945, Reed and Helwig[48] reviewed 300 cases of infectious mononucleosis and found evidence of anemia in 6 patients. They felt that the anemia was the result, in some instances, of infectious granulomatous infiltration of the bone marrow; however, late reports have shown that the bone marrow is either normal or shows hyperplasia of the erythroid elements in infectious mononucleosis (Custer and Smith[16], Wisner[66]). The fact that the bone marrow is normal is, at times, quite helpful when problems of differential diagnosis arise. The possible mechanisms for the hemolytic anemia may be summarized as follows. Archer and Hall found evidence of a circulating agglutinin active against red blood cells of all groups[26], and postulated the cause to be either 1) destruction of red blood cells by disease or overactive spleen (this may be a cause in some cases but reports of cases of hemolytic anemia with hemoglobinuria [Kirkham[34]] suggest an intravascular process in some); 2) action of the virus may produce hemagglutinins (this is difficult to prove since the virus itself has not been isolated); and 3) possible formation of hemolytic immune bodies (the reported response to cortisone supports this view in some instances).

Since the above reports, there have been cases reported dealing with inherent defects in the red blood cells themselves (Bean[2], Thurm and Bassen[60]). The view is expressed that, in addition to the above concepts, infectious mononucleosis may exacerbate some inherent abnormality in the red cells, thus producing an anemia. Hemolysis, as a rule, begins early in the course of the disease with sudden, explosive onset and is usually self-limited. The Coombs' test may or may

not be positive, and the view is expressed that when the Coombs' test is negative the process is a result of hypersplenism. Steroids have been reported to be of value in reports by Hall and Archer[26], and were of unquestionable value in Case 1, presented above.

While it has been recognized for some time that a mild bleeding tendency, characterized by epistaxis, ecchymoses, petechiae and hematuria, may be associated with infectious mononucleosis (Bernstein[4], Tidy and Daniel[61]), severe bleeding episodes and thrombocytopenia have been considered rare; but recent reports of bleeding episodes with massive rectal bleeding, hemoptysis and hematuria, and severe thrombocytopenia associated with infectious mononucleosis have appeared (Copeman[15]). Grossman and Pader[45], in 1956, reviewed 300 cases and found thrombocytopenia occurring in only 2 cases, or an incidence of 0.7%. The bone marrow has been found to contain normal or increased numbers of megakaryocytes (Custer and Smith[16], Freeman *et al.*[22]). These authors felt that a platelet antibody was responsible for the thrombocytopenia and hypothesized the formation of a platelet antibody as a result of combination of a virus agent of infectious mononucleosis with the platelets in certain susceptible patients. This may well be an important factor since it has been shown that platelet agglutinating factors are present in certain cases of infectious mononucleosis (Freeman *et al.*[22]). It is also possible that latent cases of idiopathic thrombocytopenic purpura may be exacerbated by infectious mononucleosis (Pader and Grossman[45]). It appears that true idiopathic thrombocytopenic purpura may be ruled out in these cases, however, since the bleeding tendency disappears as the infectious process clears up.

CARDIAC COMPLICATIONS. Most observers have felt that the cardiac manifestations of infectious mononucleosis are, as a rule, subclinical and manifested only by transient electrocardiographic abnormalities (Miller, Uricchio and Phillips[43], Roseman and Barry[51]). It has been stated "Myocardial lesions which have been seen are rarely severe enough to cause more than transient electrocardiographic abnormalities" (Houck[30]). Necropsy reports (Custer and Smith[16]) have shown cardiac involvement in 6 out of 9 cases. The changes have consisted of aggregates of lymphocytes distributed in the myocardium within the periphery of small blood vessels but no actual muscle necrosis and no pericarditis; however, in a recent report (Fish and Barton[21]), there was evidence of infiltration and inflammatory cells in the myocardium with focal areas of necrosis of the myocardium. This occurred in a fatal case of infectious mononucleosis with acute myocarditis, thus strengthening the impression that severe cardiac abnormalities may be produced by infectious mononucleosis. In an analysis of 100 cases of infectious mononucleosis by electrocardiograms, only 5% of these tracings were considered abnormal, the abnormalities being prolonged P–R interval, A–V block, increased Q–T duration and flattened T waves. In a review of this aspect, Webster presented 5 cases with cardiac involvement[64], in which were found either evidence of myocarditis, pericarditis or congestive heart failure in association with infectious mononucleosis, and discussed cardiac manifestations including A–V conduction blocks, S–T segment depression, apical systolic murmurs, friction rubs and congestive heart failure. Transitory bundle branch block has also been reported (Smith[57]). Recent reviews have dealt with the association of pericarditis in infectious mononucleosis (Boehm, Rose and

Barnes[8], Roseman and Barry[51], Shugoll[54], Webster[64]). The findings in these reports were those typically found in pericarditis; namely, elevated S–T segments, depression of the T waves, chest pain and friction rub and, in several cases, the manifestations of pericarditis were present several days days before those of infectious mononucleosis. The conclusion drawn from these reports is that infectious mononucleosis is probably one of the etiologic agents of acute nonspecific or idiopathic pericarditis, and should be considered when such a case occurs.

Summary. Infectious mononucleosis may present in a large variety of guises, or its clinical course may be complicated by involvement of multiple organ systems. Five case histories illustrating some of the complications of infectious mononucleosis are detailed. These include a fatal encephalitis, a peripheral neuropathy, a transverse myelitis, and an acute hemolytic crisis. In addition, the case of a young child presenting the differential diagnosis between acute leukemia and infectious mononucleosis is discussed.

The presenting complaint and complications of infectious mononucleosis depend upon the major organ system involved and particularly within the central nervous system, the area chiefly involved. The literature is reviewed on the complications and some of the factors involved discussed.

Unusual neurologic signs and symptoms and bizarre hematologic pictures occurring particularly in teen-agers should be considered as being due possibly to infectious mononucleosis.

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REFERENCES

1. **Asworth, J.**, and **Motto, S. A.**: New England J. Med., **237**, 544, 1947.
2. **Bean, R. H. D.**: Med. J. Australia, **1**, 386, 1957.
3. **Bercel, N.**: Am. J Med. Sci., **224**, 667, 1952.
4. **Bernstein, A.**: Medicine, **19**, 85, 1940.
5. **Bernstein, A.**, and **Wolfe, H.**: Ann. Int. Med., **33**, 1120, 1950.
6. **Betts, C.**, **Sickert, R.**, and **Clark, E.**: Proc. Mayo Clinic, **31**, 413, 1956.
7. **Blausten, A.**, and **Caccavo, A.**: Arch. Ophthal., **43**, 853, 1950.
8. **Boehm, W.**, **Rose, W.**, and **Barnes, H.**: Illinois Med. J., **98**, 260, 1950.
9. **Briggs, J.**, **Bellomo, J.**, and **Zauner, R.**: Dis. Chest, **30**, 557, 1956.
10. **Burke, A. V.**, and **Davis, W. D.**: Am. J. Digest. Dis., **2**, 430, 1957.
11. **Canter, H.**, and **Schillhammer, W.**: U.S. Armed Forces Med. J., **8**, 1670, 1957.
12. **Cohn, C.**, and **Lidman, B. I.**: J. Clin. Invest., **25**, 145, 1946.
13. **Connell, J.**, and **Clifton, S.**: Australian & New Zealand J. Surg., **27**, 49, 1957
14. **Coogan, I.**, **Martinson, D.**, and **Matthews, W.**: Illinois Med. J., **87**, 296, 1945.
15. **Copeman, R.**: Med. J. Australia, **2**, 925, 1956.
16. **Custer, R. B.**, and **Smith, C. B.**: Blood, **3**, 830, 1948.
17. **Dameshek, W.**: J. Am. Med. Assn., **123**, 77, 1943.
18. **Dixon, R.**: Illinois Med. J., **102**, 316, 1952.
19. **Downey, H.**, and **McKinley, C.**: Arch. Int. Med., **32**, 82, 1923.
20. **Epstein, S. H.**, and **Dameshek, W.**: New England J. Med., **205**, 1238, 1931.
21. **Fish, M.**, and **Barton, H.**: A.M.A. Arch. Int. Med., **101**, 636, 1958.
22. **Freeman, T.**, **Oxon, B.**, **Wakefield, G.**, and **Lond, M.**: Lancet, **2**, 883, 1958.
23. **Frenkel, E.**, **Shiver, C.**, **Berg, P.**, and **Carris, T.**: J. Am. Med. Assn., **162**, 885, 1956.
24. **Gilbert, R. L.**: Wisconsin Med. J., **48**, 925, 1949.
25. **Green, I.**: Neurology, **5**, 366, 1955.
26. **Hall, D. D.**, and **Archer, F. C.**: New England J. Med., **249**, 923, 1953.
27. **Hoagland, R.**: Am. J. Med. Sci., **232**, 252, 1956.

28. **Hoct, P.,** and **Caird, F.:** Brit. Med. J., **1,** 85, 1958.
29. **Hollister, L., Houck, G.,** and **Dunlap, W.:** Am. J. Med., **20,** 643, 1956.
30. **Houck, G.:** Ibid., **7,** 699, 1949.
31. **Jordan, W. S.,** and **Allbright, R. W.:** J. Lab. & Clin. Med., **35,** 688, 1950.
32. **Kallos, A.:** A.M.A. Arch. Dermat. & Syph, **69,** 618, 1954.
33. **Karpe, G.,** and **Wising, T.:** Acta ophthal., **26,** 19, 1948.
34. **Kirkham, L. J.:** Iowa State Med. J., **45,** 525, 1955.
35. **Klein, M.:** Confinia Neurol., **14,** 232, 1954.
36. **Krasnow, S.:** Illinois Med. J., **113,** 94, 1958.
37. **Lawrence, J. S.:** *In* Cecil's Textbook of Medicine, 8th ed. Philadelphia: W. B. Saunders Co., pp. 71–73, 1951.
38. **Liebowitz, S.,** and **Brody, H.:** New England J. Med., **8,** 675, 1950.
39. **Marshall, S.,** and **Millingen, K. S.:** Brit. Med. J., **1,** 1325, 1952.
40. **Mackey, R. D.,** and **Wakefield, E. G.:** Ann. Clin. Med., **4,** 727, 1926.
41. **Melville, H.:** Med. J. Australia, **1,** 356, 1955.
42. **Mhyre, J.:** J. Lab. & Clin. Med., **34,** 1671, 1949.
43. **Miller, H., Uricchio, J. F.,** and **Phillips, R. W.:** New England J. Med., **249,** 36, 1953.
44. **Nelson, R.,** and **Darragh, J.:** Am. J. Med., **21,** 26, 1956.
45. **Pader, E.,** and **Grossman, H.:** New York State Med. J., **56,** 1905, 1956.
46. **Pew, W.:** Northwest Med., **56,** 695, 1957.
47. **Pfeiffer, E.:** Jahrb. f. Kinderh., **29,** 257, 1889.
48. **Reed, J. T.,** and **Helwig, F. C.:** Arch. Int. Med., **75,** 376, 1945.
49. **Rennie, L.,** and **Wroblewski, F.:** New England J. Med., **257,** 547, 1957.
50. **Riske-Nielsen, E.,** and **Mogensen, E.:** Acta hematol., **13,** 387, 1955.
51. **Roseman, D.,** and **Barry, R.:** Ann. Int. Med., **47,** 351, 1957.
52. **Shecket, H.:** Ohio State Med. J., **51,** 863, 1955.
53. **Shiver, C., Berg, P.,** and **Frenkel, E.:** J. Am. Med. Assn., **161,** 592, 1956.
54. **Shugoll, G.:** A.M.A. Arch. Int. Med., **100,** 630, 1957.
55. **Silverstein, J., Bernstein, T. C.,** and **Stern, T.:** J. Lab. & Clin. Med., **33,** 1204, 1948.
56. **Smith, J. N.:** Ann. Int. Med., **44,** 861, 1956.
57. **Smith, R.:** California Med., **87,** 39, 1957.
58. **Stevens, J.:** Virginia Med. Month., **79,** 74, 1952.
59. **Tanner, O. R.:** A.M.A. Arch. Ophthal., **51,** 229, 1954.
60. **Thurm, R.,** and **Bassen, F.:** Blood, **10,** 841, 1955.
61. **Tidy, H. C.,** and **Daniel, E. C.:** Lancet, **2,** 9, 1923.
62. **Vander, J.:** Ann. Int. Med., **41,** 146, 1954.
63. **Wagman, G.:** A.M.A. Arch. Path., **64,** 457, 1957.
64. **Webster, B.:** Am. J. Med. Sci., **234,** 62, 1957.
65. **Wechsler, H. F., Rosenbloom, A. H.,** and **Sills, C. T.:** Ann. Int. Med., **25,** 113, 1946.
66. **Wisner, H. J.:** J. Kansas Med. Soc., **53,** 566, 1952.
67. **Wolfe, L.,** and **Fine, J.:** Wisconsin Med. J., **50,** 869, 1951.
68. **Wormer, D., Martin, W.,** and **Wollaegen, E.:** Ann. Int. Med., **45,** 718, 1956.

(Interlingua on page 719)

PRIMARY H. INFLUENZAE PNEUMONIA IN AN ADULT WITH EXTREME HYPERPYREXIA

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A 49-year-old Negress with primary *H. influenzae* pneumonia is presented. The last group of primary adult pneumonias due to this organism, numbering 3 cases, was reported by Crowell and Loube[4] in 1954. These constituted in an 8-year hospital series less than 0.1% of all pneumonias. In the patient here presented, bacteremia was accompanied by an extreme temperature elevation (108.2°). Furthermore, the illnesses commonly predisposing to this disease, namely, viral respiratory infection and bronchiectasis, were absent. An opportunity was thus presented to examine the clinical course of pneumonia in an adult where *H. influenzae* was the primary etiologic agent and the resultant illness severe.

Case Report. This 49-year-old colored housemaid was admitted to the Greenwich Hospital on April 23, 1957, complaining of chilliness. At 2 a.m. on the day of admission she awakened from her sleep with a headache and nausea. She vomited once and took an aspirin for her headache with no relief. When seen at home, a tentative diagnosis of intestinal grippe was made. During the day she had cleaned the cellar, which was damp and cold. She had no cough or chest pain. Neck stiffness was not present. Facilities for home care were not available and the patient was hospitalized.

Her past medical history was noncontributory. She had never been married. She had worked as a domestic for many years. There was no history of recurrent respiratory infections. Also negative was any history of pneumonia, rheumatic fever, and central nervous system disease. Operations included removal of a neck cyst and a hysterectomy.

At 10:30 a.m. on the day of admission the patient's rectal temperature was 99.8°, pulse regular at 110 to 120, respirations 20 per minute. Her blood pressure was 112/80. She was well-oriented and cooperative. She complained of leg muscle pain and continued nausea. There was no cough. On examination no cyanosis or dyspnea was detectable. The pharynx appeared normal. The neck was supple. The lungs showed complete absence of rales or rhonchi. Expiratory prolongation suggested mild emphysema. Heart sounds were somewhat distant, but sinus tachycardia as above was the only significant finding. Abdominal muscles showed some voluntary rigidity. However, no abnormal organ enlargement was present. Neurological examination was negative throughout; abnormal reflexes could not be elicited. Pelvic examination performed several days later was negative. The uterus was absent in keeping with her history.

The initial white blood count was 11,400, which rose to 26,000 on the second day and to the peak level of 31,800 on the third, after which there was a gradual decrease. The leukocytosis was polymorphonuclear. Urine study on admission showed 4-plus albumin as the only abnormal finding. The albuminuria decreased almost daily, reverting to normal in a week. Blood chemistry including sugar, bilirubin and electrolytes was not significantly altered. Serum albumin and globulin were normal and the VDRL slide flocculation for syphilis was negative. The blood urea nitrogen remained normal except for a transitory rise to 30 mg. per 100 ml. on the second hospital day. Sedimentation rates were 40 to 50 mm. per hr.

A dramatic alteration in the clinical picture occurred in the first 24 hours of hospitalization. After a sharp temperature rise, which reached 103.4° at noon and returned to normal at 8 p.m., the temperature rose abruptly so that by midnight it was 106.0° and despite iced alcohol rub-down and ice water enemas, climbed to 108.2° by 2 a.m. This reading represents an extrapolation from the upper limit on the rectal thermometer which has markings to 108°. At this point 100 mg. of cortisone was given intravenously and 200 mg. intramuscularly. The fall in temperature was prompt and sustained. It was 101.0° by noon the next day and never exceeded this level for the remainder of the

illness, reaching normal levels on the third hospital day.

At the height of the temperature rise the patient vomited a small amount of clear fluid. She also had four loose stools, caused in part by the ice water enemas. Also a voluntary muscular spasm of the right arm developed which gradually relaxed as the temperature fell. No abnormal reflexes appeared; pupils reacted normally. The neck remained supple throughout. The patient was rational and answered questions accurately. She complained of nausea, thirst and chilliness, although no frank chill was observed. She remained restless and alert until the temperature dropped, when she fell asleep. The following morning intermittent nystagmoid movements were demonstrated. These disappeared within hours. Lumbar puncture at this time was noncontributory in regard to cell count, protein, sugar, chlorides, and colloidal gold curve. Spinal fluid pressures were not increased.

Blood "febrile" agglutinins, which include Typhoid O and H, Paratyphoid B and H, *B. abortus*, and Proteus OX-19, did not achieve significant titers. Throat culture showed alpha streptococci, and catheterized urine culture slowly grew out *E. coli* and *B. subtilis*. Two separate blood cultures taken during the first two temperature rises were both positive for a small Gram negative cocco-bacillus identified later as *H. influenzae* Type B by the Neufeld reaction.

Fig. 1.—Chest film on 3rd hospital day with bronchopneumonia in lower two-thirds of the right lung field.

Throughout the illness the pharynx remained normal in appearance and neither laryngeal nor bronchial signs developed. There was no cough. On the third day rhonchi and rales were heard at the right base. Signs of frank consolidation did not develop. Chest roentgenogram on the day of admission was suggestive of "bronchopneumonic infiltration" at the right base. On the third hospital day a repeat film showed bronchopneumonia in the lower two-thirds of the right lung field, as illustrated (Fig. 1).

On the second hospital day, as the temperature was returning to normal levels, shock intervened with blood pressures approximately 68/50, shallow respirations, and a weak rapid pulse of 120 to 140 per minute. A cardiogram at this time was essentially normal. Noradrenalin was started intravenously and additional cortisone given. The patient was placed in oxygen. By evening the blood pressure was

until it constituted the patient's chief complaint. Roentgenogram of the knees showed only "minor hypertrophic changes of the patella." The pain seemed muscular. No objective signs of infection or arthritis appeared. The pain and accompanying tenderness remained localized, finally fading gradually away. Salicylates did not appear to affect its course. No other site became involved.

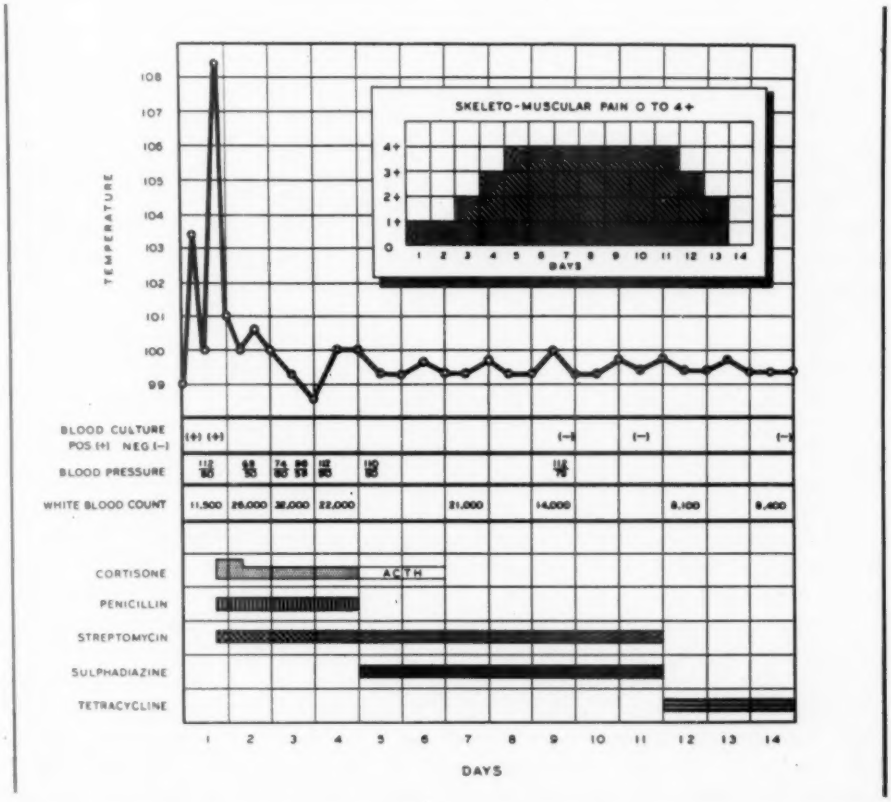

Fig. 2.—Graphic summary of clinical course showing length of time therapeutic agents were used; also pertinent clinical findings. Insert represents approximate grading of skeleto-muscular pain. Note peak severity follows remission of fever.

normal. Noradrenalin was withdrawn the following day and cortisone was reduced and then discontinued on the fourth hospital day. Two injections at daily intervals of ACTH Gel were then given.

Severe right knee pain radiating into the anterior thighs appeared on the fourth day. Some pain in this region had been present almost since the beginning. It increased now

Streptomycin was administered in daily doses of 2 gm. in combination with penicillin until the third day when the etiology became clear. Streptomycin was then continued for 7 more days in combination with sulphadiazine, which was given in 3-gm. daily doses; the penicillin having been discontinued. Finally, Achromycin, 1 gm. a day, was added the final 4 days of hospitalization

by itself to obviate the possibility of residual infection or recurrence (Fig. 2).

All observers agreed that no mental deterioration had been caused by the extreme hyperpyrexia. Psychometrics were not done, but repeated lengthy questioning could demonstrate no defect in memory, orientation, or speed of response. Her ability to do simple sums seemed intact. An old friend of the patient's could not observe any significant change on the mental or emotional level. Subjectively there was no feeling of dullness, amnesia, or easy emotionalism. Upon discharge on the fifteenth hospital day, all signs and symptoms of illness had disappeared.

Discussion. *Hemophilus influenzae* pneumonia is commonly described as having no distinctive clinical picture (Dowling[6], Hinshaw and Garland[12]). Certain general tendencies are recognized: that such pneumonia may be grave (Dowling[6]); that vulnerability to *H. influenzae* infection of any kind decreases from early childhood (Fothergill and Wright[8]); and that respiratory disease, particularly of viral origin, predisposes to this kind of pneumonia (Dowling[6]). Aside from this, descriptions of the clinical features vary widely, appearing at times contradictory. Even the frequency of the occurrence of *H. influenzae* pneumonia is not easily determined (Nichols and Andersen[15]). There are several explanations for this. As mentioned, epidemics of respiratory grippe-like illnesses seem to predispose to this type of pneumonia and raise its attack rate spasmodically (Dowling[6]). Also, *H. influenzae* exhibits a definite tropism toward the bronchi and upper respiratory tract. The severe ulcerative bronchitis sometimes seen may dominate the clinical picture and small patches of pneumonia escape notice. In Dowling's series, these pneumonias accounted for 0.3% of the total number[6], but whether in these cases the *H. influenzae* organism was the primary etiologic agent, or an invader secondary to some other derangement in the immunity mechanism is not stated. Primary *H. influenzae* pneumonia was found in fewer than 0.1% of pneumonias in an 8-year hospital series (Crowell and Loube[4]). A final difficulty in determining the incidence of the disease is the increasing use of streptomycin and the tetracyclines early in the course of pneumonic infections. Positive cultures are undoubtedly missed in this way, and the resultant illness sharply modified. Thus some pneumonias considered "viral" may well be of this origin.

The possible severity of *H. influenzae* pneumonia is emphasized by several sources (Dowling[6], Durant *et al.*[7], Hall[9]). High fever is considered common, also cough, dyspnea, hemoptysis and pleural pain. Durant *et al.*[7] reiterate that bronchiectasis may predispose to this illness, and complicate its management. The organism frequently attacks the upper respiratory tract and the bronchi, and sticky sputum, like that associated with Friedlander's pneumonia, may be present (Dawber and Hawes[5]). That the lung alone may be involved is illustrated by this patient. It is not now thought, as formerly, that administration of penicillin worsens the outlook by stimulating an overgrowth of Gram negative organisms (Hinshaw and Garland[12]). But lack of response of a pneumonia to penicillin may be taken as a suggestive finding. Special media are required for *H. influenzae* culture growth; recently these have been further improved (Hall[9]).

In *H. influenzae* pneumonia, the temperature elevation, as mentioned, may be marked, but the level achieved here (108.2°) in an adult in response to infection of any kind is, of course, distinctly unusual (Harrison[11]). The apparent avoidance subsequently of central nervous system damage in this patient is also of interest. Partly responsible was the relatively brief duration

of fever over 105°, about 3 to 4 hours. It was cortisone alone that effected the fever's remission after the traditional methods had failed. In turn, this allowed time for the antibiotics to achieve therapeutic levels. Whether other factors were involved in sparing the brain is not clear. Racial differences in regard to temperature regulation have been noted; for example, in the relative ease with which certain forms of artificial fever may be induced in whites as compared with Negroes. Whether the latter are less vulnerable to the central nervous system effects of high temperature remains unknown. In this patient, except for a voluntary kind of rigidity of one arm at the height of the fever and transitory nystagmoid movements the next morning, neurological signs including those expressing frontal lobe function remained entirely absent. Shock occurred on the third hospital day. This is a more common finding in this clinical context than the extreme fever. Hall and Goll correlate shock in infections with the presence of bacteremia[10]. They found significant hypotension in 10% of pneumococcic pneumonias. In this patient, the overwhelming nature of her infection as expressed by her fever, leukocytosis, sedimentation rate, and the like, might alone have caused shock.

It appears unsettled whether *H. influenzae* pneumonia is characteristically lobar or bronchial. The patchy bronchopneumonia exhibited by this patient is the kind described by most authorities (Dowling[6], Harrison[11], Hinshaw and Garland[12]). However, in a recent textbook on diseases of the chest, Bunn and Eastman classify *H. influenzae* and pneumococcic pneumonia together, both in regard to their ability to achieve "complete resolution" and in their lobar distribution[14]. Also rather strikingly, all four primary *H. influenzae* pneumonias of Crowell and Loube were lobar pneumonias[4]. Perhaps it may be concluded that neither distribution of infection is entirely characteristic of this organism, and furthermore that clinical distinctions between these types is not always possible.

The definitive diagnosis is entirely dependent on the demonstration of the organism: in the blood, as here, or in large numbers in the sputum. Small numbers of *H. influenzae* in the pharyngeal flora, even of the more significant type B variety, may cause no illness. Other laboratory findings are at the most suggestive. Dowling, for example, states that the white count may be normal, slightly elevated or slightly low[6]. The 32,000 white cell count found in this patient no doubt reflected the unusual severity of her illness. When present, the leukocytosis, as here, is polymorphonuclear. Similarly the patient's initial 4 plus albuminuria, which gradually faded, correlated well with the degree of the severity of the infection. A transitory rise in blood urea nitrogen coincided with the onset of shock; its origin thus appeared to be prerenal.

In reviewing the literature we were struck by the emphasis Crowell and Loube placed on severe skeleto-muscular pain which they found in all 3 adults in their series[4]. It is the only instance where a relationship between pain of this kind and *H. influenzae* pneumonia was suggested. Muscular pain is possible, of course, in any severe infectious illness, and their case reports do not include very detailed descriptions of the pain; they were mainly impressed with its consistency as a finding and its severity. In our patient the pain had the following characteristics: a) It was localized, remaining in the right knee and thigh. It neither decreased in area nor spread

into neighboring muscles before it disappeared. No other site became involved. b) There was a paucity of objective signs, some slight swelling, no heat, slight tenderness. Full range of motion was maintained. A roentgenogram of the knee was noncontributory. c) It was severe; it constituted the chief complaint of an otherwise stoical patient during most of her hospital stay. Salicylates were ineffective and the height of the pain did not correlate with the severity of the pneumonia. It would be of interest if other observers found severe skeleto-muscular pain more frequently in pneumonias caused by this organism.

The emphasis of most recent writing about this illness has been upon treatment. We have considered the clinical features at greater length, because once the diagnosis is established, the treatment has become generally very effective. The infection responds to a wide variety of antibiotics (Harrison[11], Hinshaw and Garland[12], Nichols and Andersen[15]) and to sulfadiazine. We employed the latter in combination with streptomycin. This was followed by a brief course of tetracycline therapy because of the possibility that infections of this severity may be complicated by empyema or meningitis. Durant *et al.* first demonstrated the efficacy of streptomycin in this disease[7]. Where bronchiectasis was a complication the unpurified drug was used intratracheally with success. The tetracyclines have the advantage over streptomycin of rarely inducing resistant strains (Alexander and Leidy[1], Austrian[2]); they are often adequate alone (Love and Finland[13]). In an overwhelming infection such as this one, the corticoids may be invaluable as adjuvants to the antibiotics, especially where fever, as here, is extreme. It would seem finally that the most effective prophylaxis would include: The extensive use of influenza vaccine, and the adequate management of bronchiectasis. In the latter regard Dowling and his associates have recently felt that the prophylactic suppression of *H. influenzae* when it is present by means of daily antibiotics is of importance[3]. These measures would probably have less influence on primary *H. influenzae* pneumonia; the latter appears fortunately to be an uncommon disease.

Summary. A case of primary bacteremic *H. influenzae* pneumonia in an adult is presented. The case is of particular interest in that severe hyperpyrexia (108.2°) occurred at the height of the disease necessitating corticoid therapy in addition to multiple antibiotics.

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REFERENCES

1. **Alexander, H. E.,** and **Leidy, G.:** J. Exper. Med., **85**, 329, 1947.
2. **Austrian, R.:** J. Am. Med. Assn., **163**, 1040, 1957.
3. **Cherniak, N. S., Vosti, K. L., Dowling, H. F., Leppes, M. H.,** and **Jackson, G. G.:** A.M.A. Arch. Int. Med., **103**, 345, 1959.
4. **Crowell, J.,** and **Loube, S.:** Ibid., **93**, 921, 1954.
5. **Dawber, T. R.,** and **Hawes, L. E.:** Diseases of the Chest. Baltimore: The Williams & Wilkins Company, p. 336, 1952.
6. **Dowling, H. F.:** The Acute Bacterial Diseases. Philadelphia: W. B. Saunders Co., p. 355, 1948.
7. **Durant, T., Sokalchuk, A. J., Norris, C. M.,** and **Brown, C. L.:** J. Am. Med. Assn., **131**, 194, 1946.

8. **Fothergill, L. D.,** and **Wright, J.:** J. Immunol., **24,** 281, 1933.
9. **Hall, W. H.:** Med. Clin. N. America, **43,** 201, 1959.
10. **Hall, W. H.,** and **Goll, D.:** A.M.A. Arch. Int. Med., **96,** 403, 1955.
11. **Harrison, T. R.:** Principles of Internal Medicine, 3rd ed. New York: McGraw-Hill Book Company, p. 72, 1958.
12. **Hinshaw, H. C.,** and **Garland, L. H.:** Diseases of the Chest. Philadelphia: W. B. Saunders Company, p. 111, 1956.
13. **Love, B. D.,** and **Finland, M.:** J. Pediat., **45,** 531, 1954.
14. **Naclerio, E. A.:** Bronchopulmonary Disease. New York: Paul B. Hoeber, Inc., p. 333, 1957.
15. **Nichols, D. R.,** and **Andersen, H. A.:** Med. Clin. N. America, **38,** 981, 1954.

SUMMARIO IN INTERLINGUA

Pneumonia Primari a *Hemophilus influenzae* in un Adulto con Hyperexia Extreme

Es presentate un caso de primari pneumonia bacteremic a *Hemophilus influenzae* in un patiente adulte. Le caso es de interesse particular in tanto que hyperexia sever (108,2 F.) occurreva al culmine del curso clinic, de maniera que un therapia corticoide esseva necessari a parte le uso de multiple antibioticos.

SUMMARIO IN INTERLINGUA

(See page 699 for original article)

Complicationes de Mononucleosis Infectiose

Mononucleosis infectiose se manifesta in variissime modos, e su curso clinic pote esser complicate per affectiones in multo diverse systemas organic. Es presentate in detalio cinque casos que illustra certes del complicationes de mononucleosis infectiose. Le serie include un caso de encephalitis mortal, un de neuropathia peripheric, un de myelitis transverse, e un de acute crisis hemolytic. Es discutite in plus le caso de un patiente pediatric in qui le diagnose differential esseva un question de leucemia o mononucleosis infectiose.

Le gravamine initial e le complicationes de mononucleosis infectiose depende de qual major systema organic es afficite e particularmente de qual area intra le systema nervose central es principalmente interessate. Es presentate un revista del litteratura concernite con le complicationes de mononucleosis infectiose. Certes del factores pertinente es discutite.

Inusual signos neurologic e un bizarre situation hematologic, occurrente specialmente in adolescentes, debe esser considerate como possibilemente causate per mononucleosis infectiose.

MANAGEMENT OF PATIENTS RECEIVING WARFARIN SODIUM (COUMADIN)* THERAPY WITH PROTHROMBIN TIME DETERMINATIONS AT 3-DAY INTERVALS

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Present recommendations for the initiation of anticoagulant therapy with coumarin drugs demand that prothrombin times be checked daily until a stabilized dose-response relationship is established. Once this is achieved, the prothrombin may be measured less frequently, with a resulting saving in laboratory expense and reduction in the trauma of frequent venipunctures. It is the purpose of this paper to report on a group of patients in whom prothrombin times were not taken daily during initial phases of treatment, although warfarin sodium (Coumadin) was given each day. Prothrombin times were usually determined at 3-day intervals, and warfarin sodium was used as the anticoagulant in all cases. A previous attempt (Clatanoff and Meyer[2]) at anticoagulant therapy wherein prothrombin times were measured at 3-day intervals and single doses of warfarin sodium given every third day was thought to be unsatisfactory owing to wide fluctuation of prothrombin levels over the 3-day periods.

That some patients may show erratic responses to warfarin sodium during the first weeks of therapy while others show stable and predictable responses has been common experience. Escapes from therapeutic levels of hypoprothrombinemia once a maintenance dose has been established are infrequent, and rapid determination of this dose is obviously desirable. Too frequent manipulation of dosage may be one of the difficulties preventing prompt assessment of the daily dose for maintenance in any patient. It has been suggested (Toohey[8]) that a clearer picture of the exact maintenance requirements for warfarin sodium could be obtained if the treatment were assessed over 3-day periods.

Also, it was suggested by Dr. Samuel M. Gordon[5] that if patients were properly selected it might be possible to choose those destined to show a predictable response, and to regulate the anticoagulant dosage at 3-day intervals from the onset of therapy in these patients. With this in mind, a retrospective study of patients who had been treated with warfarin sodium was undertaken, and it was found that predictable responses were to be expected from the beginning of therapy if the following patients were excluded from consideration: 1) those less than 14 days postpartum or postoperative; 2)

*Supplied by Endo Laboratories, Inc., Richmond Hill, New York, through the courtesy of Dr. Samuel M. Gordon.

those given heparin as well as a coumarin; 3) those showing a sensitive or resistant response to an initial 50-mg. dose of warfarin sodium as manifested by a fall in prothrombin to below 17% or a failure to drop below 45% within the first 42 hours; 4) those with pretreatment prothrombin levels below 100%; 5) those taking neither food nor liquids by mouth; 6) those who were already receiving anticoagulant therapy at the time of their hospital admission; and 7) the critically ill, especially those with prolonged hypotension after myocardial infarction.

Materials and Methods. Of 91 patients treated at the University Hospitals with an anticoagulant over a 6-month period there were 38 in whom initial intermittent control of therapy was not attempted because they fell in one of the seven categories above. An additional 15 patients were not included in this report because of inadequate records, dosage errors, or a treatment period of less than 6 days. The remaining 38 make up the group here reported upon. They were observed for from 6 to 63 days, with an average duration of treatment of 17 days. Indications for anticoagulant therapy in the group of patients were: myocardial infarction, 14; thrombophlebitis, 10; cerebrovascular disease, 9; atrial fibrillation with embolization, 4; and prophylaxis during conversion of atrial fibrillation, 1.

Prothrombin times were obtained in all cases before the anticoagulant was given. All patients with a normal prothrombin time were then given a 50-mg. dose of warfarin sodium. The initial doses were always given at 4:00 p.m. so that approximately 42 hours would elapse before the morning of the second day following commencement of treatment, when blood for the next prothrombin determination was drawn. On the basis of this prothrombin time, doses of the drug to be administered daily at 4:00 p.m. for the next 3 days were ordered, according to the following schedule:

Prothrombin Time (seconds)	*Prothrombin (%)*	*Daily Warfarin Sodium Dose (mg.)*
Over 28	Less than 17%	Less than 5 mg. (daily prothrombin times ordered)
28 to 22	17% to 25%	5 mg.
21 to 20	27% to 30%	7.5 mg.
19 to 18	33% to 35%	10 mg.
17	40%	12.5 mg.
16	45%	15 mg.
Below 16	More than 45%	15 mg. or more (daily prothrombin times ordered)

The prothrombin time was next measured on the morning following the last of the 3 days for which warfarin sodium had been ordered. The uniform daily dose of the drug to be given for the next 3 days was based on this result, with the following criteria used as criteria for dosage. If the level of hypoprothrombinemia was near or above the upper limit of the therapeutic range (17 seconds or 40%), the daily dose of warfarin was usually increased by 2.5 mg. No change of dosage was made if the prothrombin level underwent little change during the preceding 3-day period and if the prothrombin time was near the mid-point of the therapeutic range (20 seconds or 30%). A definite decrease in the prothrombin level or a prothrombin time below the lower limit of the therapeutic range (25 seconds or 20%) usually indicated a 2.5 mg. reduction in the daily dose of warfarin sodium. Occasionally dosage changes of 5 mg. per day were made in the face of larger changes in prothrombin levels. This process was repeated at 3-day intervals until sufficient stabilization occurred to allow further reduction in the frequency of prothrombin time determinations.

Any gross deviation from the desired levels of hypoprothrombinemia was considered an indication to resort to daily prothrombin time determinations for re-regulation. This was done in only one case where an unex-

pectedly prolonged prothrombin time occurred on the seventh day of treatment.

Occasionally some deviation of a day from the schedule of every third day was allowed in order to decrease the work of the laboratory on Sundays and holidays. In 7 of the patients observed during the first phases of this study prothrombin times were obtained daily, but dosage of the drug was changed only at 3-day intervals, and the daily figures were not allowed to bias the planned scheme.

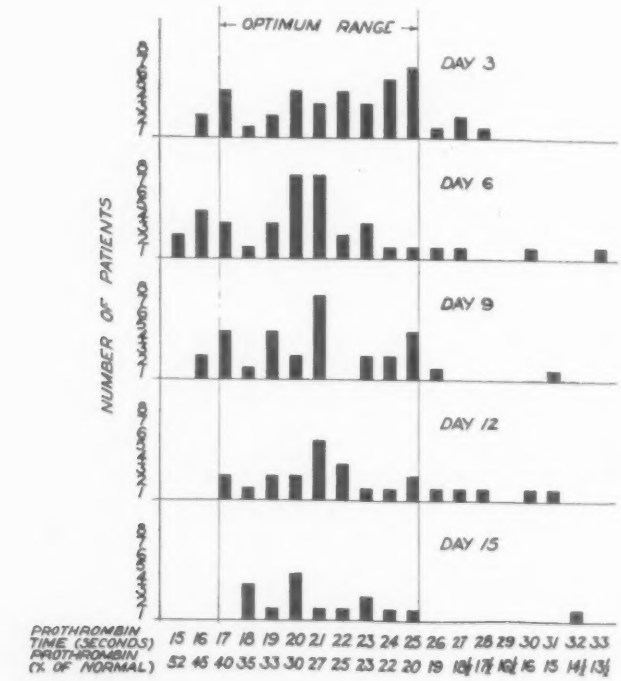
← OPTIMUM RANGE →
DAY 3
DAY 6
DAY 9
DAY 12
DAY 15
NUMBER OF PATIENTS
PROTHROMBIN TIME (SECONDS) 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32 33
PROTHROMBIN (% OF NORMAL) 52 45 40 35 33 30 27 25 23 22 20 19 18½ 17½ 16½ 16 15 14½ 13½

Fig. 1.—Prothrombin times at 3-day intervals for the patients in this series through the first 15 days of treatment.

Determination of prothrombin times was done on undiluted plasma by the one-stage method of Quick, with the use of Difco thromboplastin (rabbit brain). The control prothrombin times, with rare exceptions, were 12 seconds (100%) and all determinations were done or supervised by the same technician. Blood for the prothrombin time determinations was drawn between 8:30 and 10:00 a.m.

Results. Figure 1 depicts the prothrombin times on all patients through the first 15 days of treatment. The row marked day 3 indicates prothrombin times 40 to 42 hours after the initial 50-mg. doses of warfarin sodium. Prothrombin times of less than 16 seconds or more than 28 seconds are not shown, since patients with these times were no longer candidates for treatment with this 3-day schedule.

The 6 patients whose prothrombin rose to above 40% after the first 3-day maintenance treatment period had prothrombin times within the therapeutic range 3 days later. In one of these 6 the initial daily doses were smaller than the recommended amounts. In 2 others there was suspicion that a dose of warfarin sodium had been inadvertently omitted. Two patients had prothrombin levels above

40% on the 12th and 15th days; and, of the patients followed beyond this time, there were only 4 whose prothrombin level ever rose above 40%. There were no thromboembolic episodes in any patient of the group after commencement of the anticoagulant therapy.

The safe lower limit of hypoprothrombinemia was considered to be 20%. Four patients had prothrombin levels below 20% on the third and on sixth days of therapy. This occurred in 2 on the ninth day, 5 on the 12th day, one on the 15th day, and in the group followed beyond 15 days only 3 ever developed a hypoprothrombinemia below 20%. Two minor bleeding episodes occurred. One man developed a subconjunctival hemorrhage the day after therapy was started. This resolved normally in spite of continued anticoagulation and was thought not to have been related to the therapy. A small ecchymosis was noted above the right ankle in another patient. Her prothrombin was 30% on the day this occurred.

Figures 2, 3, 4, and 5 show representative examples of dosage and response in patients in this series. Two indicate very stable responses to uniform dosage, while the other 2 illustrate responses to changes in dosage.

In this series the average daily maintenance dose of warfarin sodium for all patients was 7 mg. We found no clear-cut correlation between the body weight and optimal dosage.

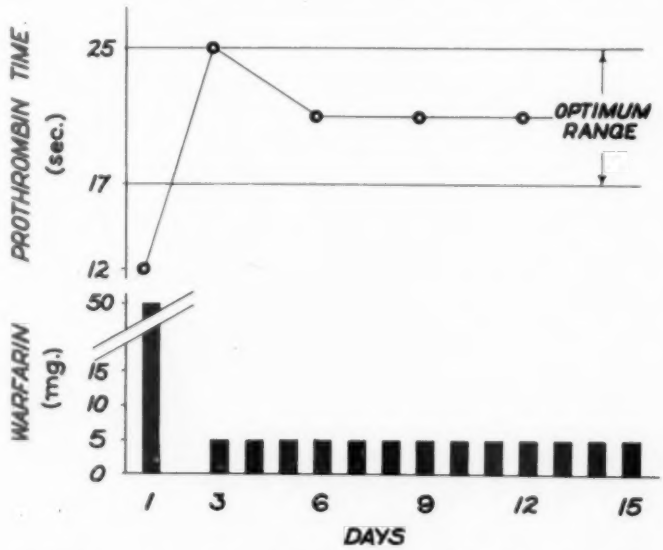

Fig. 2.—Stable hypoprothrombinemia with a 5-mg. daily dose of warfarin sodium (patient E.G.).

Discussion. The data indicate that satisfactory control of the plasma prothrombin when warfarin sodium is used can be achieved in selected patients with prothrombin values used as guides to dosage at intervals of 3 days. Comparison of these data with those of other authors is very difficult because of differences in control prothrombin times and acceptance of different prothrombin percentages as proper therapeutic levels. In one series

of patients (Danford, Juergens and Barker[3]) treated with warfarin sodium, escape from the therapeutic range of hypoprothrombinemia occurred on only 5% of total days of treatment. Three other reports (Baer *et al.*[1], Fremont and Jagendorf[4], Nicholson and Leavitt[6]) describing experience with warfarin sodium indicated a satisfactory level of anticoagulation in 93% of the days under therapy, 83.5% of patients in the therapeutic range 70% of the time, and optimal prothrombin depression in 54% of total maintenance

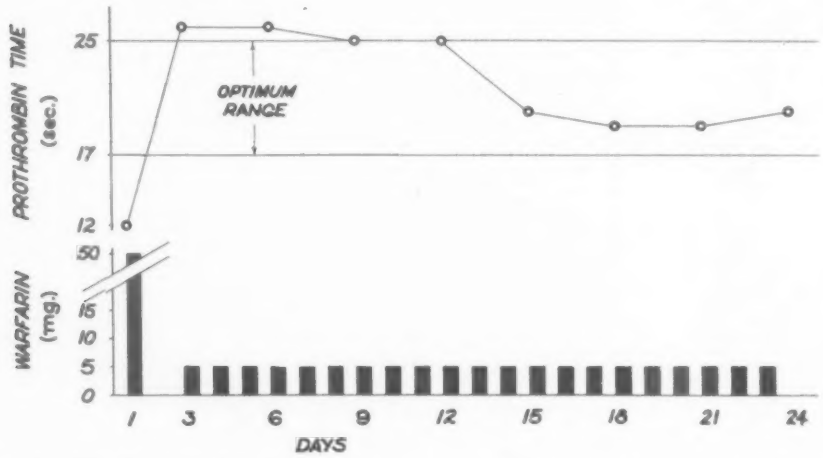

Fig. 3.—Initially stable hypoprothrombinemia followed by a change and re-stabilization with a 5-mg. daily dose of warfarin sodium (patient M.R.).

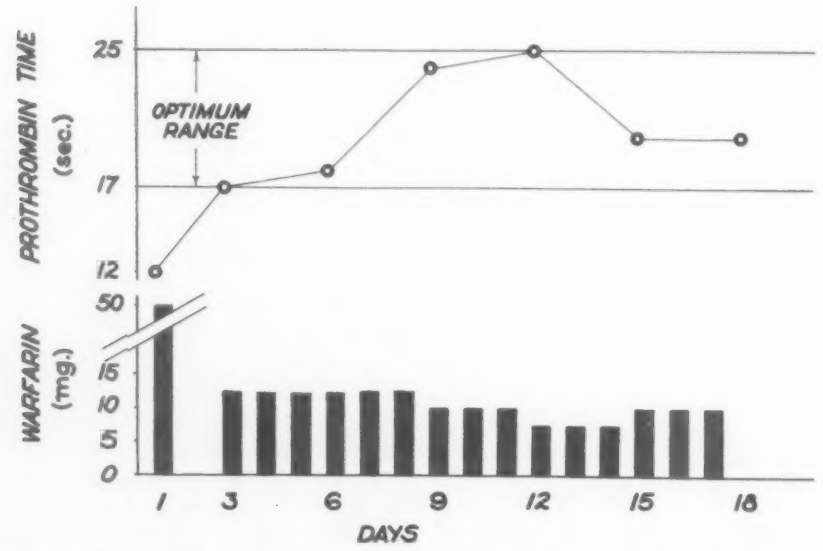

Fig. 4.—Prothrombin times at 3-day intervals with varying dosage of warfarin sodium (patient D.H.).

days with suboptimal (therapeutic levels) on 37% of the days. In our series, 82% of prothrombin times measured between the third and the fifteenth day of therapy were within the therapeutic range, and 94.5% were below 40%, which is considered to be the upper limit of therapeutic hypoprothrombinemia. While these results cannot be strictly compared to those in other series, it is concluded that the comparison is favorable.

before one attempts to base his treatment on intermittent prothrombin times. If these qualifications have been met, however, properly selected patients can be well regulated with warfarin sodium without the need for daily prothrombin times. In many patients it would seem perfectly practical after the first 9 to 12 days to do prothrombin times semi-weekly, perhaps on Mondays and Thursdays or Tuesdays and Fridays.

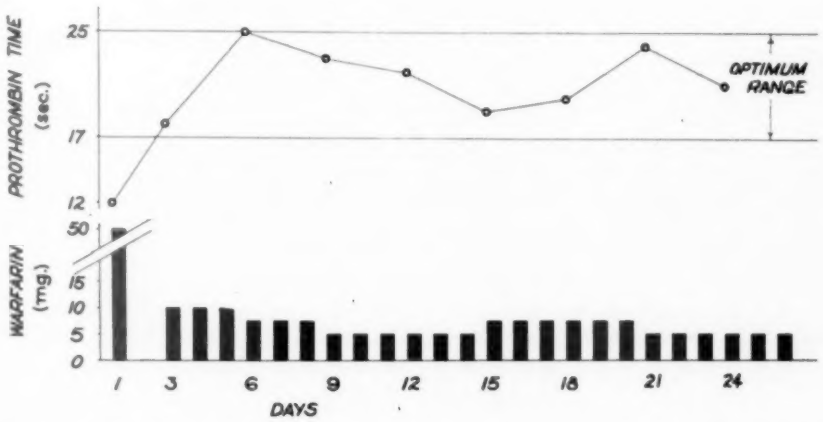

Fig. 5.—Prothrombin times at 3-day intervals with varying dosage of warfarin sodium (patient W.J.).

Although it was thought that the management of patients receiving warfarin sodium was advantageous when 3-day intervals were used for assessment and adjustment of dosage, we would not suggest that all acceptable patients be treated in this way from the onset of their anticoagulant therapy. It is realized that a spurious result of any prothrombin determination will have an undue effect upon management, since dosage for 3 days rather than one will be based on it. Thus, a high degree of laboratory accuracy is essential. Some experience with coumarins in a variety of patients needing anticoagulation should be obtained

It has been suggested (Porter, Richardson and Mauck[7], Toohey[8]) that the proper initial dose for starting most patients on anticoagulant therapy with warfarin sodium should be in the neighborhood of 50 mg. In this dosage range 95% of patients were found to be in the therapeutic range in 36 hours in one study (Toohey[8]). Maximal prothrombin depression will persist for between 36 and 48 hours after an initial 50-mg. dose of warfarin sodium. Thus, measurement of the prothrombin time at 40 to 42 hours after the initial dose gives an indication of the patient's actual maximal response and a good

indication of what his future dose response relationship will be. Once maintenance therapy is begun, time must be allowed so that the effect of small changes in dosage will be demonstrated, and it was for this reason that 3-day intervals were chosen. The recommendation for adjustments in dosage of 2.5 mg. comes from the fact that Coumadin (warfarin sodium) is supplied in 5, 10, and 25 mg. tablets, and 2.5 mg. quantities are easily obtained by breaking the scored 5 mg. tablets.

Summary. Thirty-eight selected patients were successfully managed on anticoagulant therapy with warfarin sodium (Coumadin), with prothrombin time determinations done at 3-day intervals. Fifty-milligram doses of warfarin sodium (Coumadin) were used to initiate the therapy in all patients. A decrease in laboratory costs and lessening of the need for frequent venipunctures are obvious advantages resulting from less frequent prothrombin time measurements.

ACKNOWLEDGMENT: We wish to express our thanks to Miss Mary K. Dahnke for her technical assistance.

REFERENCES

1. **Baer, S., Yarrow, M. W., Kravitz, C.,** and **Markson, V.:** J. Am. Med. Assn., **167,** 704, 1958.
2. **Clatanoff, D. V.,** and **Meyer, O. O.:** A.M.A. Arch. Int. Med., **97,** 753, 1956.
3. **Danford, H. G., Juergens, J. L.,** and **Barker, N. W.:** Proc. Staff Meet., Mayo Clin., **33,** 359, 1958.
4. **Fremont, R. E.,** and **Jagendorf, B.:** J. Am. Med. Assn., **165,** 1381, 1957.
5. **Gordon, S. M.:** Personal communication.
6. **Nicholson, J. H.,** and **Leavitt, T., Jr.:** New England J. Med., **255,** 491, 1956.
7. **Porter, R. R., Richardson, D.,** and **Mauck, H. P., Jr.:** Virginia Med. Month., **85,** 465, 1958.
8. **Toohey, M.:** British Med. J., **2,** 892, 1958.

SUMMARIO IN INTERLINGUA

Un Programma de Determinationes del Tempore de Prothrombina a Intervallos de Tres Dies in le Tractamento de Patientes Recipiente Warfarina a Natrium (Coumadina)

Trenta-octo patientes seligite in un gruppo tractate con warfarina a natrium (Coumadina) como agente anticoagulatori esseva manipulate a bon successo con determinationes del tempore de prothrombina a intervallos de 3 dies. Doses de cinquanta milligrammas del droga esseva usate in omne le patientes pro initiar le therapia. Le resultante reduction del costos laboratorial e le reducite frequentia del requirite venipuncturas es obvie avantages del minus frequente determinationes del tempore de prothrombina.

SERUM LIPIDS IN MULTIPLE SCLEROSIS*

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Numerous investigations of serum lipid levels in multiple sclerosis have been reported during the last 30 years. The basis for such researches has usually been the supposition that the demyelination process might somehow be reflected as an aberration of serum lipids. Any such relationship, if established and recognizable, might be indicative of a metabolic disturbance, and perhaps useful in diagnosis. The results obtained by various workers have been reviewed recently by Persson[12] and discussed in relation to his own observations. In this collected body of data there are conflicts in both numerical values and conclusions. These variations have several obvious causes, including the use of different clinical material, different analytical methods, and different statistical procedures. If only the work done since about 1950 is considered, there is somewhat greater consistency in the numerical data, but discrepancies remain. There is at least one claim of a significant difference in multiple sclerosis for each of the following lipid measurements: total cholesterol, phospholipids, and total lipids. Jones, Jones, and Bunch[7] for example, found a distinct elevation of cholesterol levels in multiple sclerosis. Bernsohn and Namajuska[1] reported phospholipid levels (in 17 patients) to be somewhat lower than normal. Persson's data[12] are purported to show that in males the elevation of total lipids is significant at the 5% level. On the other hand, the bulk of evidence has seemed increasingly to indicate that in multiple sclerosis none of the lipid components differs significantly from normal. Our own results, reported here, support this view.

While our results are perhaps no more definitive than some of the other sets of data that have been reported, they are offered for consideration in regard to whatever uncertainty remains concerning the lipid relationships in multiple sclerosis. Our analyses were made by a novel method, employing infrared spectrophotometry of total lipid extracts from serum. Determinations were obtained of total lipids, total phospholipids, total cholesterol, and total esterified fatty acids. This method has been previously described in tentative form[5], and many of the analyses included in the present study were used in the further evaluation of its validity. Our control data were obtained at the same time and by the same procedure. This is not true for

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several of the reports cited from the literature.

Material and Method. SAMPLING. Serum samples from 43 multiple sclerosis patients were analyzed. The 19 males and 24 females ranged in age from 25 to 74 years, with an average age of 44 years. Approximately half of the total number were institutionalized at Laguna Honda Home, San Francisco, California. In all subjects the disease was in the active phase at the time of sampling. Blood samples were drawn during the fasting state, and serum was prepared in the usual way.

TABLE 1.—MEAN SERUM LIPID CONCENTRATIONS (MG./100 ML.) FOR NORMALS AND MULTIPLE SCLEROSIS PATIENTS, ALL AGES

	Normals (Ages 21–62, Av. 35)				*Multiple Sclerosis (Ages 25–66, Av. 44)*			
	N	*Range*	*Mean*	*S.D.*	*N*	*Range*	*Mean*	*S.D.*
Total lipids	37	486–1191	739	155	43	539–1091	740	141
Cholesterol*	36	160–340	232	40	43	159–389	248	47
Phospholipids	36	156–334	220	37	43	201–361	253	41
Esterified fatty acids	35	225–606	382	85	43	298–627	398	79

*The normal group is a sample of a much larger normal population for which serum cholesterol measurements by chemical methods are available. For 818 males of ages 30 to 39 years, the average cholesterol value is 226.4 mg. per 100 ml., with a standard deviation of 43.5 mg. per 100 ml.

Corresponding analytical data were obtained for 37 healthy individuals, 29 of whom were males and 8 females. They ranged in age from 21 to 62 years, with an average of 35 years.

ANALYTICAL METHOD. A total lipid extract was prepared from 1 ml. of serum by the procedure of Sperry and Brand[15]. The extract obtained in this way has been shown to be quantitative with respect to lipids and at the same time substantially free of nonlipid impurities. The total lipid was dissolved in a measured volume (in the range 0.6 to 0.8 ml.) of carbon tetrachloride, and the infrared absorption curve of this solution was recorded in the spectral range from 5 to 10 microns. (The instrument used was a Baird double-beam spectrophotometer equipped with a sodium chloride prism. The absorption cell had a path length of 0.9 mm.) Using absorbances measured for peaks near 5.8, 6.8, 7.25, and 9.15 microns, and previously determined calibration coefficients for those wavelengths, values for the various lipid components were computed as described by Freeman[5]. Further evaluation of the infrared method since that preliminary report has shown that in general its reproducibility is within about ± 5% for all components measured. Agreement with chemical methods is within ± 10% for cholesterol and fatty acids. Total lipids measured by infrared agree with weights within ± 3%. Our phospholipid values are generally higher than chemical determinations by about 5 to 15%. Inasmuch as our comparison of multiple sclerosis patients and normals is based on results obtained with the same method, any differences observed are related to the precision of that method rather than to its absolute accuracy.

Results. The data are presented as frequency histograms in Fig. 1. The numerical descriptions of these distributions are summarized in Table 1. Except for total lipids, the average lipid values are slightly higher for multiple sclerosis patients than for normals. However, it has by now been rather well established that serum lipids tend to increase with age (Keys *et al.*[9], Peterson[13], Lindholm[11]). Since the average age of the disease group is greater than the average age of normals by 9 years, this factor may account for at least part of the observed small differences in lipid values. To test

this hypothesis, a selection of the data has been made from the two groups for the age range 30 to 39 years and compared. The overall average age of normals is in the middle of the 30 to 39 year interval, and it may be seen from Tables 1 and 2 that the average lipid values for the narrow age range are essentially unchanged from the corresponding averages for all ages. In the multiple sclerosis group, however, average lipid values for the selected range

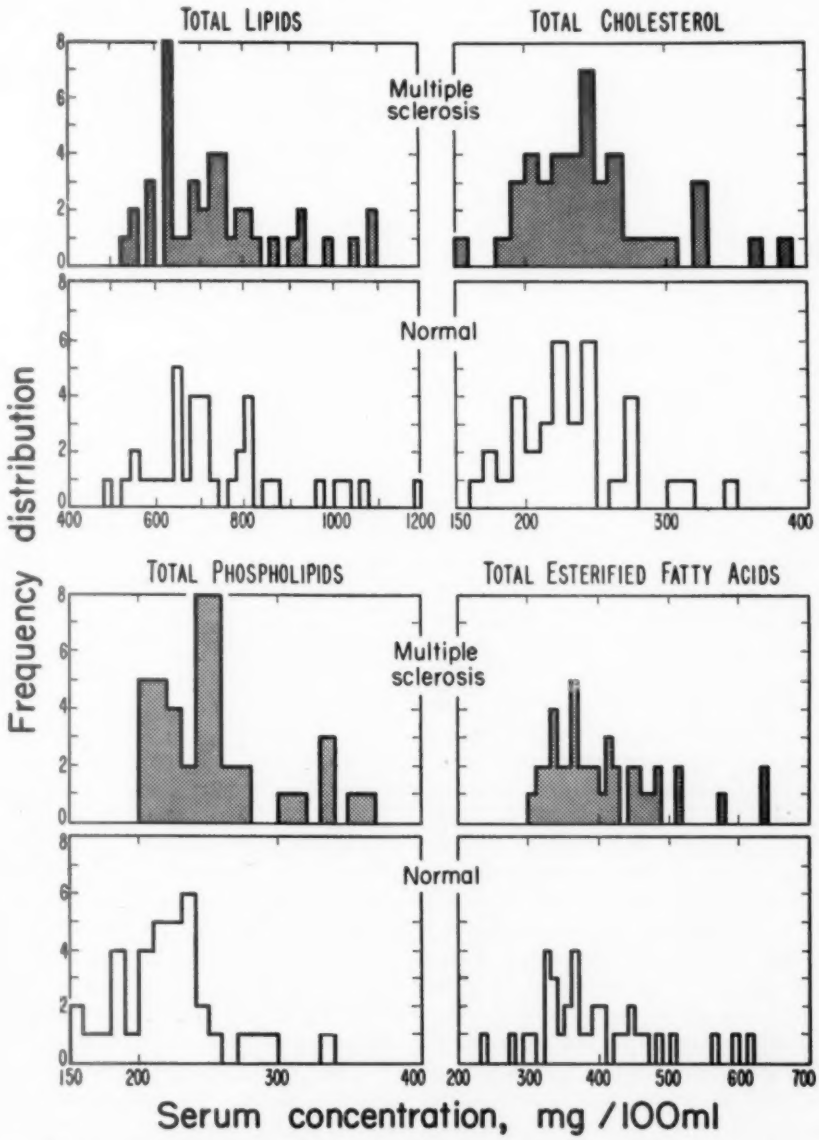

Fig. 1.—Distributions of serum lipid concentrations in multiple sclerosis patients and in normal individuals. (See also Table 1.)

are consistently lower than the corresponding averages for all ages. If age-adjusted averages (Table 2) are now compared between normal and multiple sclerosis groups, the largest percentage difference (which is in phospholipids) can be shown not to be significant at the 5% probability level.

TABLE 2.—MEAN SERUM LIPID CONCENTRATIONS (MG./100 ML.) FOR NORMALS AND MULTIPLE SCLEROSIS PATIENTS, AGES 30–39 ONLY

	Normals (N = 19)		*Multiple Sclerosis (N = 15)*	
	Range	*Mean*	*Range*	*Mean*
Total lipids	593–1012	735	546–934	707
Cholesterol	193–318	234	190–296	237
Phospholipids	158–284	224	201–308	243
Esterified fatty acids	312–584	391	302–503	379

Discussion. Table 3 presents a summary of pertinent data from the literature (since 1950, except for the normal values of Kornerup[10], used for reference by Persson[12]). Our own results have been appended for comparison. Included in the table are the previously mentioned findings of serum lipid abnormalities in multiple sclerosis by Jones, Jones and Bunch[7], Bernsohn and Namajuska[1], and Persson[12]. In addition, Dobin and Switzer[3] have stated that in their 58 multiple sclerosis patients statistically significant numbers of both cholesterol and lipid phosphorus values were elevated above the accepted normal ranges for those measurements. Their limits for normal ranges were believed to have been chosen so as to represent "unequivocally normal values." However, the basis of this evaluation was not given, and it is perhaps questionable to assume, as they seem to have done, that all serum cholesterol values above 250 mg. per 100 ml. are abnormal.

The data which indicate no essential difference with respect to serum lipids in multiple sclerosis and in health are those of Chiavacci and Sperry[2], Wilmot and Swank[16], Jones *et al.*[8] (phospholipids) Roboz *et al.*[14] (total lipids), Persson[12] (except for total lipids), Jeanes and Cumings[6] (cholesterol), and the present study. Note that in Table 3 our values are those for the entire age range, not those for the selected age group. It was also stated by Fog[4] that he found no differences in cholesterol, lipid phosphorus, or neutral fat, although he did not present data or indicate the number of cases studied.

In addition to the components listed in Table 3, free cholesterol was determined by some investigators (Chiavacci and Sperry[2], Dobin and Switzer[3], Fog[4], Jeanes and Cumings[6], Persson[12], Wilmot and Swank[16]) with no findings of abnormalities in multiple sclerosis. Neither have any abnormalities been indicated for neutral fat, although this component has been defined differently in different reports (Persson[12], Wilmot and Swank[16]). Our data (Table 1) include measurements of total esterified fatty acids, which could be combined with other lipid values to give computed triglyceride concentrations. Since the

TABLE 3.—SUMMARY OF COMPARATIVE DATA FOR SERUM LIPIDS IN MULTIPLE SCLEROSIS

(Mean value ± Standard deviation, mg. per 100 ml. of serum)

Reference		*N*	*Total Lipids*	*Cholesterol*	*Phospholipids*
Jones *et al.*[7]	Normal	30		240 ± 40	
	M S	25 (Relapse)		271 ± 35	
		38 (Remission)		267 ± 43	
Jones *et al.*[8]	Normal	80			251 ± 39
	M S	108			245 ± 35
Chiavacci and Sperry[2]	Normal			201 ± 45	
	M S	52		203.5 ± 47.2	210 ± 43
Wilmot and Swank[16]	Normal	14	591(477–722)	188(112–241)	214(177–268)
	M S	15	639(486–765)	194(140–244)	218(176–272)
Dobin and Switzer[3]	Normal	(Ranges assumed)	(400–800)	(125–250)	(200–275)
	M S	58	683 ± 140	229 ± 52	261 ± 67
Roboz *et al.*[14]	Normal		463 ± 57		
	M S	8	471 ± 67		
Bernsohn and Namajuska[1]	Normal	14			248 ± 32
	M S	17			221.5 ± 38
Persson[12] (Normal Values from Kornerup[10])	Normal	58	829 ± 181	217 ± 42	185 ± 35
	M S	32 (Males)	891 ± 95	234 ± 44	197 ± 33
Jeanes and Cumings[6]	M S	20(Active)		204(125–250)	
This Study	Normal	35	739 ± 155	232 ± 40	220 ± 37
	M S	43	740 ± 141	248 ± 47	253 ± 41

Note 1. Numbers enclosed in parentheses indicate ranges of values.

Note 2. Wherever lipid phosphorus figures were given in the original reports, they have been converted to phospholipid values by multiplying with the factor 25.

fatty acids are substantially the same in both groups, and inaccuracies are likely to be compounded in carrying out such calculations, we have not considered it worthwhile to do so. Individual classes of serum phospholipids (lecithin, cephalin, and sphingomyelin) were measured by Jones *et al.*[8] in 23 multiple sclerosis patients and 25 healthy controls (matched for age and sex). No differences were observed in any of the phospholipid classes. Measurements by Bernsohn and Namajuska[1] also indicated normal distributions of phospholipids in multiple sclerosis, although total phospholipids were low.

Summary. Blood sera from 43 multiple sclerosis patients have been analyzed for total lipids, total cholesterol, total phospholipids, and total esterified fatty acids by an infrared spectrophotometric method. Corresponding measurements have been made for 37 healthy individuals. These two sets of data have been compared with each other and with other earlier results of other investigators.

When an age-matched selection of the data is made, none of the averages for measured serum lipid components in multiple sclerosis patients is significantly different from the corresponding average for healthy persons.

While there are some conflicting conclusions in the literature with regard to possible serum lipid abnormalities in multiple sclerosis, our findings are in agreement with the majority of recent evidence on this point.

ACKNOWLEDGMENT: Grateful acknowledgment is made to Dr. Herbert D. Krall, Medical Director, Laguna Honda Home, and to Drs. William J. Wedell and William W. Anderson of the University of California School of Medicine, San Francisco, for making available blood specimens of multiple sclerosis patients.

REFERENCES

1. **Bernsohn, J.**, and **Namajuska, I.**: Proc. Soc. Exper. Biol. & Med., **88**, 124, 1955.
2. **Chiavacci, L.**, and **Sperry, W.**: A.M.A. Arch. Neurol. and Psychiat.,**68**, 37, 1952.
3. **Dobin, N. B.**, and **Switzer, J. L.**: A.M.A. Arch. Neurol. and Psychiat., **71**, 405, 1954.
4. **Fog, T.**: Acta psychiat. et neurol. Scandinav.; Supplement 74, 22, 1951.
5. **Freeman, N. K.**: Ann. New York Acad. Sci., **69**, 131, 1957.
6. **Jeanes, A. L.**, and **Cumings, J. N.**: Confin. Neurol., **18**, 397, 1958.
7. **Jones, H. H.**, **Jones, H. H., Jr.**, and **Bunch, L. D.**: Ann. Int. Med., **33**, 831, 1950.
8. **Jones, H. H.**, **Jones, H. H., Jr.**, **Howard, R. R.**, and **Bunch, L. D.**: Ann. New York Acad. Sci., **58**, 656, 1954.
9. **Keys, A.**, **Nickelsen, O.**, **Hayes, R.**, and **Miller, E.**: Fed. Proc., **9**, 69, 1950.
10. **Kornerup, V.**: Nord, Med., **16**, 3300, 1942.
11. **Lindholm, H.**: Scandinav. J. Clin. & Lab. Invest., **8**, Supp. 23, 1956.
12. **Persson, I.**: Acta psychiat. et neurol. Scandinav., **33**, 197, 1958.
13. **Peterson, V. P.**: Acta med. Scandinav., **146**, 375, 1953.
14. **Roboz, E.**, **Hess, W.**, **Forster, F.**, and **Temple, D.**: A.M.A. Arch. Neurol. and Psychiat., **72**, 154, 1954.
15. **Sperry, W. M.**, and **Brand, F. C.**: J. Biol. Chem.; **213**, 69, 1955.
16. **Wilmot, V.**, and **Swank, R. L.**: Am. J. Med. Sci., **223**, 25, 1952.

(Interlingua on page 739)

RESPONSE TO CAROTENE LOADING IN MALABSORPTION STATES

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and

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Low serum levels of fat-soluble vitamins, particularly carotene, are characteristic of the malabsorption syndrome in man (Cayer, Ruffin and Perlzweig[4], Adlersberg, Wang and Bossak[2]). The level of circulating carotene is a reflection of intake and absorption since the nutrient is not stored in the body. An earlier study (Adlersberg *et al.*[1]) suggested defective carotene absorption in malabsorption states. Therefore, an extended systematic study was undertaken of effects of carotene loading in patients with this disorder.

Materials and Methods. Serum carotene was determined by the spectrophotometric micro method of Lowry and Bessey[3]. Blood specimens were drawn and analyzed prior to and 1 2, 3, 4 and 7 days after administration of 120 mg. (200,000 I.U.) of crystalline carotene† (90% beta-carotene, 10% alpha-carotene) mixed in 20 gm. of butter spread on bread or crackers. Subjects were not required to be fasting prior to venipuncture. Foods high in carotene were avoided for the week of the test. All patients were ambulatory.

The carotene loading test was performed in 9 healthy control subjects and in 16 patients with various malabsorption syndromes. Eight women and 2 men with nontropical sprue were symptomatically controlled on steroid therapy; one woman each had tropical sprue, celiac disease in remission, nontropical sprue in remission without therapy, intestinal lipodystrophy under good control, and previous pancreatectomy for carcinoma; one man had had a massive small intestine resection for extensive jejuno-ileitis.

Serum vitamin A concentration (Bessey *et al.*[3]) was determined prior to and 4, 6 and 8 hours after administration of 180,000 I.U. of vitamin A. Quantitative analysis of fat in a 72-hour stool collection (Van de Kamer, ten Bokkel Huinink and Weyers[11]) was also performed. In addition, studies of vitamin B_{12} absorption utilizing the Schilling test[9] in the modification of Oxenhorn *et al.*[7] were performed in 11 patients.‡

Results. Initial levels of serum carotene in the control group ranged from 70 to 228 μg. per 100 ml. with a mean level of 141 μg. per 100 ml. (Fig. 1, Table 1). Results are comparable to levels reported earlier in 9 control individuals (Adlersberg *et al.*[1]). After administration of the carotene load, serum levels rose in all control subjects with an increment ranging from 26 to 81 μg. The mean increment was 46 μg. In the "old" series, the mean increment was 50 μg. Peak levels in the present study ranged from 100 to 304 μg. per 100 ml. The peak level was reached on day 1 in one subject, day 2 in 2 subjects, day 3 in 4 subjects, day 4 in one subject and day 7 in one subject. The majority reached the peak by the 3rd day.

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†Obtained in single dose ampules from General Biochemicals, Inc., Chagrin Falls, Ohio, and stored in dark, closed containers at 4° C.

‡We should like to thank Drs. S. Estren and S. Oxenhorn for providing these data.

TABLE 1.—CAROTENE LOADING TEST IN HEALTHY CONTROL SUBJECTS AND PATIENTS WITH MALABSORPTION SYNDROME COMPARED WITH VITAMIN A TOLERANCE TEST, FECAL FAT EXCRETION AND URINARY EXCRETION OF LABELED B_{12}

	Carotene Level							*Vitamin A level*				
				μg. per 100 ml.			*Increment*	*μg. per 100 ml.*		*Increment*	*Fecal Fat*	*Labeled B_{12} Excretion*
Group	*Day* 0	1	2	3	4	7	*μg.*	0	*Peak*	*μg.*	*gm/day*	%
Mean control	132	168	174	163		141	48	87	210	123	<5	18
Present control	141	169	176	179	172	160	46					(9–36)
Old control	122	166	172	147		122	50					
Nontropical Sprue	24	30	30	30	31	30	10	69	83	18	27.0	2.1
Tropical Sprue	23	28	28	28	32	32	9	47	99	52	6.2	
Celiac disease remission	128	139	138	138	147	128	19	43	72	29	3.7	4.2
Nontropical Sprue remission	140	164	168	170	153	166	30	117	665	548	2.1	9.5
Intestinal Lipodystrophy	78	83	81	78	78	85	7	86	622	536	5.1	
Pancreatectomy	13	13	13	14	14	18	5	42	47	5	26.1	
Intestinal Resection	7	7	8	10	6	6	3	74	220	146	96.5	0.1

In the patients with nontropical sprue, initial levels of serum carotene ranged from 11 to 48 μg. with a mean level of 24 μg. per 100 ml. (Fig. 1, Table 1). After administration of carotene load serum carotene levels were unchanged in one patient, rose less than 5 μg. in 5 patients, rose 5 and 9 μg. in each of 2 patients, rose 28 μg. in one patient and 43 μg. in one patient with the rare coincidence of diabetes mellitus and sprue. The mean increment was 10 μg. (6 μg. if the last is excluded). Peak levels ranged from 12 to 50 μg. per 100 ml. excluding the last patient in whom the carotene peak was 82 μg. per 100 ml.

Results in the remaining 6 patients are presented individually in Table 1. Levels obtained in the patient with tropical sprue were similar in all respects to those with nontropical sprue. The patient with celiac disease in remission had initial and peak carotene levels within the normal range with a low increment of 19 μg. The results obtained in the patient with nontropical sprue in remission fell within the normal range in all respects (Fig. 1). The patients with intestinal lipodystrophy, post-pancreatectomy and post-intestinal resection showed minimal absorption of carotene. In the latter two instances, levels were very low while in the

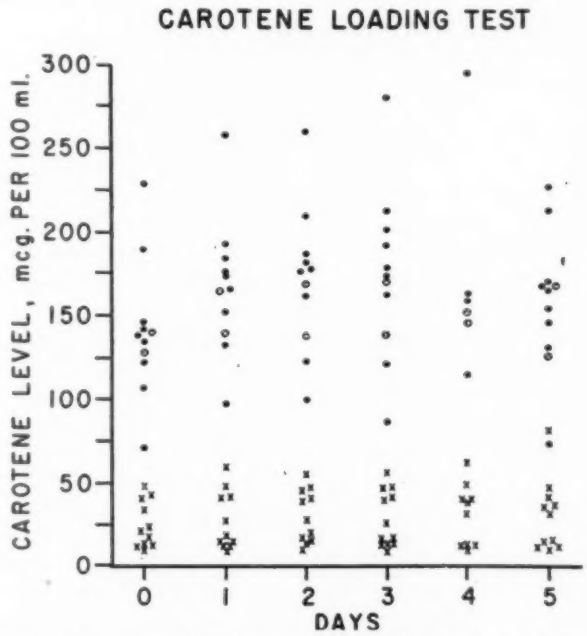

Fig. 1.—Serum carotene concentration determined daily for one to 7 days following carotene loading on day 0.

Symbols:
• Healthy control persons (9)
X Patients with nontropical sprue (10) or tropical sprue (1)
O Patients in remission from celiac disease (1) or nontropical sprue (1)

patient with Whipple's disease, levels approached the low normal range.

Fecal fat values in the group with nontropical sprue ranged from 9.7 to 63.1 gm. per 24 hours with a mean excretion of 27.0 gm. of fat per day (normal below 5 gm.) (Table 1). Fat excretion was slightly increased in the patient with tropical sprue. Normal values were obtained in the patients with asymptomatic celiac disease, nontropical sprue in remission and Whipple's disease. Marked steatorrhea was observed in the patients with previous pancreatectomy and intestinal resection.

Absorption of vitamin A was severely impaired in the group with nontropical sprue. The mean fasting level of 60 μg. per 100 ml. approached the normal (range 29 to 105 μg. per 100 ml.). The mean increment after loading, however was only 19 μg. (range 0 to 43 μg.) as compared to the normal range of 90 to 239 μg. (Adlersberg, Wang and Bossak[2]). Peak values ranged from 37 to 123 μg., values below the normal mean peak of 210 μg. per 100 ml. In the patient with tropical sprue, vitamin A absorption was moderately impaired (increment of 52 μg.). Vitamin A absorption was markedly impaired in the patients with asymptomatic celiac disease and postpancreatectomy, and was normal in the patient with previous intestinal resection. Extremely high peak levels of serum vitamin A were obtained in the patients with nontropical sprue in remission and with Whipple's disease.

Values of urinary excretion of labeled vitamin B_{12} (Schilling test) were well below normal in 7 patients with nontropical sprue. A low normal value was obtained in the patient with concomitant diabetes mellitus. A similar value was observed in the patient with sprue in remission. Low values were observed in the patient with asymptomatic celiac disease, and following massive intestinal resection.

COMMENT. Mean levels of serum carotene in the "old" and "new" series of healthy controls were in good agreement with values obtained by others. A review of the literature cited by Wenger, Kirsner and Palmer[12] yielded a mean carotene level of 169 μg. per 100 ml. These authors obtained a mean figure of 123 μg. per 100 ml. in 110 normal persons, examined by the Kimble method[6]. Their minimum normal level of 70 μg. was identical to our result.

An initial low level of serum carotene by itself served to distinguish almost all patients with malabsorption from healthy controls (Adlersberg, Wang and Bossak[2]) with the exception of the patient with active Whipple's disease.

Studies of the absorption and metabolism of carotene in man are few compared with the numerous studies performed in various animal species. Carotene is slowly absorbed in the human when given in a fat vehicle. Minimal absorption takes place on a fat-free diet (Wenger, Kirsner and Palmer[12]) while absorption from butter is much higher than from vegetable oils. Absorption from the latter can be enhanced by lecithin administration (Adlersberg *et al.*[1]). Absorption of carotene after a loading dose is slow, being measured in days rather than hours. The increment over starting levels is small, amounting to an average of 36%. Other workers demonstrated that administration of 6 mg. of carotene daily for one week increased blood carotene concentration to a similar degree while administration of doses 2 to 10 times larger raised carotene levels 100 to 200% above normal (Urbach, Hickman and Harris[10], Wenger, Kirsner and Palmer[12]). Once achieved, high levels could be maintained by a reduced

daily intake (Urbach, Hickman and Harris[10]). Administration of a single dose of 60 mg. carotene to patients with diabetes mellitus resulted in a rise of 37% (Ralli, Brandelone and Mandelbaum[8]). A similar dose given to healthy persons resulted in a rise of only 17% (Adlersberg *et al.*[1]). A flat carotene tolerance test was observed in patients with hepatitis, biliary cirrhosis, carcinoma of the pancreas and regional enteritis (Adlersberg *et al.*[1], Wenger, Kirsner and Palmer[12]). One patient with sprue studied by Wenger had normal absorption of carotene when given 20,000 units in oil daily for one week[12].

The carotene loading test in the present study was abnormal in all patients with malabsorption syndrome, using as criterion a peak level of less than 100 μg. per 100 ml. This suggests its usefulness as a diagnostic test for malabsorption despite the inconvenience of the lengthy sampling period.

The vitamin A level by itself was not of diagnostic significance in patients with malabsorption who were symptomatically controlled on steroid therapy wherein normal values were the rule. The vitamin A tolerance test, however, remained abnormal in these patients despite good clinical control, except for the patients with Whipple's disease and post-massive intestinal resection. The determination of vitamin A was technically a more tedious, difficult and time-consuming procedure than that of carotene. Since results of the carotene loading test appeared to be as good or better in detecting malabsorption and the determinations involved were simpler laboratory procedures, its comparative usefulness was enhanced.

As steatorrhea was the *sine qua non* for the diagnosis of malabsorption syndrome in the patient group, comparison of the diagnostic usefulness of fecal fat determinations with carotene absorption tests was not made. The fecal fat procedure was also difficult, that is, obtaining collections and carrying out the determinations in the laboratory. The latter criticism is nullified by using newer methods of determination of fat excretion utilizing I_{131} labeled fat (Isley *et al.*[5]). In many institutions, however, this procedure is performed only on hospitalized patients, limiting its applicability.

The Schilling test appeared as useful as the vitamin A tolerance test, since only one value in the normal range was obtained of 9 patients with malabsorption syndrome so tested. In the original study of Oxenhorn *et al.*[7], 20% of the patients showed a normal Schilling test, whereas 80% were abnormal.

Summary. A loading dose of 120 mg. of carotene was administered to 9 healthy control subjects, to 14 patients with malabsorption syndromes and to 2 patients with this disorder in remission. Serial determinations of serum carotene were performed for from 1 to 7 days following the loading dose. In the patient group vitamin A tolerance tests, quantitative fecal fat determinations, and studies of vitamin B_{12} absorption were also carried out.

In control subjects serum carotene values rose an average of 46 μg. from an initial mean level of 141 μg. to a mean peak on day 3. In patients with malabsorption syndromes serum carotene rose an average 9 μg. from an initial mean level of 26 μg. Normal initial levels were obtained in both patients in remission, with a low increment in one and normal in the other.

Steatorrhea was present in all patients except one with intestinal lipodystrophy. Vitamin A absorption was not diminished in this patient nor in one with previous intestinal resection. Vitamin B_{12} absorption was normal in one patient with sprue who also had diabetes mellitus.

An abnormal carotene loading test

was defined as one in which the peak level reached was less than 100 μg. per 100 ml. Using this criterion the results were abnormal in all patients with active malabsorption syndromes.

This suggests the usefulness of the carotene loading test as a diagnostic test for malabsorption syndrome. It has proven as good or better than the vitamin A tolerance test or Schilling test and more feasible than quantitative determination of fecal fat excretion.

ACKNOWLEDGMENTS: 1) This research was supported in part by Research Grant H-982 from the Division of Research Grants, U.S. Public Health Service; 2) We wish to acknowledge with gratitude the technical assistance of Miss Maria Torres.

REFERENCES

1. **Adlersberg, D., Kann, S., Maurer, A. P., Newerly, K., Winternitz, W.,** and **Sobotka, H.:** Am. J. Digest. Dis., **16**, 333, 1949.
2. **Adlersberg, D., Wang, C. I.,** and **Bossak, E. T.:** J. Mt. Sinai Hospital, **24**, 206, 1957.
3. **Bessey, O. A., Lowry, O. H., Brock, H. J.,** and **Lopez, J. A.:** J. Biol. Chem., **166**, 177, 1947.
4. **Cayer, D., Ruffin, J. M.,** and **Perlzweig, W. A.:** Am. J. Med. Sci., **210**, 200, 1945.
5. **Isley, J. K., Jr., Sanders, A. P., Baylin, G. J., Ruffin, J. M., Shingleton, W. W., Anlyan, W. G.,** and **Sharpe, K. W.:** Gastroenterology, **35**, 482, 1958.
6. **Kimble, M. S.:** J. Lab. & Clin. Med., **24**, 1055, 1939.
7. **Oxenhorn, S., Estren, S., Wasserman, L.,** and **Adlersberg, D.:** Ann. Int. Med., **48**, 1, 1958.
8. **Ralli, E. P., Brandaleone, H.,** and **Mandelbaum, T.:** J. Lab. & Clin. Med., **20**, 1266, 1935.
9. **Schilling, R. F.:** Ibid., **42**, 860, 1953.
10. **Urbach, C., Hickman, K.,** and **Harris, P. L.:** Exper. Med. & Surg., **10**, 7, 1952.
11. **Van de Kamer, J. H., ten Bokkel Huinink, H.,** and **Weyers, H. A.:** J. Biol. Chem. **177**, 347, 1949.
12. **Wenger, J., Kirsner, J. B.,** and **Palmer, W. L.:** Am. J. Med., **22**, 373, 1957.

SUMMARIO IN INTERLINGUA

Le Responsa al Cargation con Carotena in Statos de Malabsorption

Un dose de cargation de 120 mg de carotena esseva administrate a 9 normal subjectos de controlo, a 14 patientes con syndromes de malabsorption, e a 2 patientes con syndromes de malabsorption in stato de remission. Determinationes serial del concentration de carotena in le sero esseva effectuate durante periodos de inter 1 e 7 dies post le cargation. In le gruppos de patientes, etiam tests de tolerantia pro vitamina A, determinationes quantitative del grassia fecal, e studios del absorption de vitamina B_{12} esseva executate.

In le subjectos de controlo, le valores pro carotena seral montava al media per 46 μg ab un nivello medie initial de 141 μg, attingente le maximo al media post 3 dies. In le patientes con syndrome de malabsorption, le valores pro carotena seral montava al media per 9 μg ab un nivello medie initial de 26 μg. In ambe le patientes in stato de remission, le valores initial esseva normal. Le augmento post cargation esseva micre in le un e normal in le altere.

Steatorrhea esseva constatate in omne le patientes, con le exception de un caso in que lipodystrophia intestinal esseva presente. In iste caso, le absorption de vitamina A non esseva reducite. Similemente, illo non esseva reducite in le caso de un altere patiente con un historia de resection intestinal. Le absorption de vitamina B_{12} esseva normal in un patiente con sprue qui etiam habeva diabete mellite.

Le resultato del test de cargation con carotena esseva considerate como anormal quando le maximo del concentration de carotena effectuate in le sero remaneva infra 100 μg per 100 ml. Super le base de iste criterio, le resultatos debeva esser designate como anormal in omne le patientes con syndrome active de malabsorption.

Iste constatationes indica le utilitate del test de cargation con carotena como test diagnostic pro syndrome de malabsorption. Illo se ha provate equal o superior al test de tolerantia pro vitamina A o al test de Schilling e plus practic que le determination quantitative del excretion fecal de grassia.

SUMMARIO IN INTERLINGUA

(See page 727 for original article)

Lipidos Seral in Multiple Sclerosis

Per medio de un methodo de spectrophotometria infrarubie, seros de sanguine ab 43 patientes con multiple sclerosis esseva analysate pro lipido total, cholesterol total, phospholipidos total e esterificate acidos grasse total. Mesurationes correspondente esseva effectuate in 37 subjectos normal. Le duo corpores de datos esseva comparate le un con le altere e con previe resultatos obtenite per altere investigatores.

Quando le datos es restringite a correspondente gruppos de etate, nulle del valores medie pro mesurate componentes de lipido seral in patientes con multiple sclerosis se monstra significativemente differente ab le valores medie in subjectos normal.

Durante que le litteratura monstra certe conflictos in le conclusiones relative al possibile anormalitates de lipido seral in multiple sclerosis, nostre constatationes es de accordo con le majoritate del recente studios in tanto que iste puncto es concernite.

SUMMARIO IN INTERLINGUA

(See page 753 for original article)

Carcinoma Metastatic in le Hepate Cirrhotic

Es discutite le raritate del coexistentia de metastases hepatic con cirrhosis. Vinti-cinque casos de iste combination se trova deponite in le litteratura. Tres casos ex nostre experientia personal es addite a ille micre numero.

Certe autores hesita de includer cirrhosis biliari e metastatic carcinoma hepatic in un reporto de iste combination. Illes opina que il es impossibile negar definitemente le possibilitate del disveloppamente de metastases hepatic ante le disveloppamento del cirrhosis biliari. Un de nostre casos illustra que un simile problema pote exister in cirrhosis postnecrotic.

Le causas probabile del raritate del combination in question es discutite con citationes ab varie autores. Es interessante notar que carcinoma primari del hepate e metastases hepatic exhibi un proportion inverse. Tamen, le conclusion es formulate que le extreme raritate del coincidentia de metastatic carcinoma hepatic con cirrhosis remane un phenomeno sin explication a iste tempore.

EFFECT OF THE ADDITION OF HYDRALAZINE OR CHLOROTHIAZIDE TO GANGLIONIC BLOCKING AGENTS IN THE TREATMENT OF SEVERE HYPERTENSION

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There is considerable evidence that the life expectancy of patients with severe hypertension is increased when adequate control of the blood pressure is achieved (Schroeder, Morrow and Perry[6]). To obtain normal or near normal blood pressures in the treatment of such patients, one usually has to employ such large doses of ganglion-blocking agents as to cause many undesirable side effects. Furthermore, on this regimen, orthostatic syncope may occur if recumbent blood pressure is normalized with the result that either the physician must be less strict in his effort to control the blood pressure or the patient is inclined to abandon treatment because of fainting spells. In an effort to overcome some of these difficulties, other drugs have been added to the therapeutic regimen in the hope of reducing the dosage requirement of the ganglion blocking agents. Such combination treatments have furthermore been claimed to reduce the orthostatic blood pressure gradient and even to lead to self-sustained normotension (Perry and Schroeder[4]).

The purpose of this report is to examine the effect on orthostatic blood pressure gradient and on the dosage requirement of ganglion-blocking agent of the addition of hydralazine or of chlorothiazide to the treatment program.

Material and Methods. Severely hypertensive patients were selected with normal or borderline renal function in whom orthostatic normotension as judged by twice daily blood pressure readings in the home had been achieved with a ganglion-blocking agent. In 17 subjects it was planned to give hydralazine in increasing doses up to 400 mg. daily after which the same dose was to be maintained during a 6-month period. The dose of ganglion-blocking agent was to be adjusted as necessary to maintain continued orthostatic normotension. Four of these patients were unable to tolerate hydralazine because of headaches or edema and were thereafter maintained on ganglion-blocking agent plus placebo during the 6-month observation period. In the remaining 13, the program was carried out as planned. In 5 of these cases the effect of withdrawal of hydralazine was also studied. The lupus erythematosus cell test, sedimentation rate, gamma globulin, cephalin flocculation, albumin-globulin ratio, and complete blood count were done every 3 months on all patients receiving hydralazine.

A second group of 16 patients received chlorothiazide 500 mg. twice daily and the dose of ganglion-blocking agent was similarly readjusted to maintain orthostatic normotension. These subjects had been followed for 6 weeks at the time of this report.

Results. Table 1 summarizes the observations on the group receiving ganglion-blocking agents plus hydrala-

zine[6] or placebo. At the end of 6 months the average requirement of ganglion-blocking agent was reduced 22% as compared to 3% in the placebo group although a significant reduction was noted in only 6 of 13 subjects concluded that the additive hypotensive effects of hydralazine usually appeared, if at all, by the end of the first 6 months of therapy. The orthostatic blood pressure gradient was reduced slightly but no patients became normo-

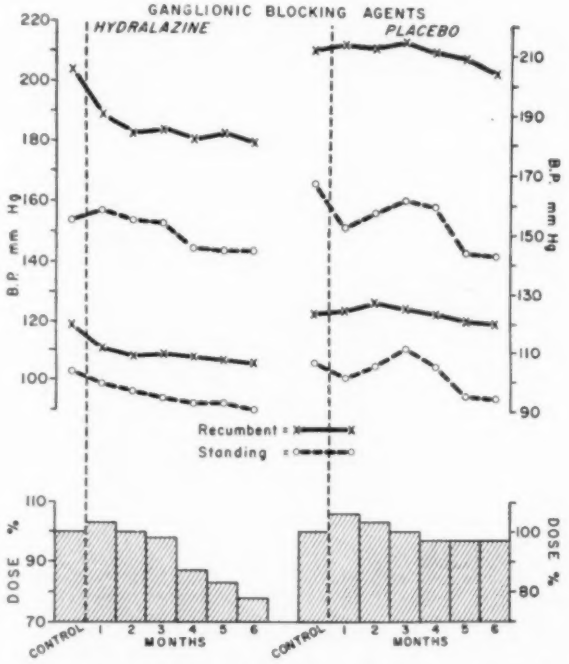

Fig. 1.—Effect of the addition of hydralazine in patients with severe hypertension treated with ganglion-blocking agents.

Each point represents the average of twice daily blood pressure readings for one month. The control period represents the blood pressure during the last 2 weeks of treatment on blocking agents alone and the dose given at this time was considered 100% for comparison with subsequent months. The amount of the blocking agent was adjusted by the patient daily, as necessary to maintain the standing systolic blood pressure near 150 mm. Hg.

It may be observed that in the group of patients in which hydralazine was added, the requirement for ganglion-blocking agent was reduced on the average by 20%.

studied. Since the reduction was found to appear in the last 3 months of this period (Fig. 1), several refractory patients were kept on the same program for an additional 2, 3, 5, and 8 months without any late reduction in the dose requirement. It could, therefore, be tensive in both standing and recumbent positions. A positive lupus erythematosus cell test or a significant change in gamma globulin, albumin-globulin ratio, cephalin flocculation or complete blood count was never observed either in the patients who did or did not

[6]We are indebted to Dr. William Wagner, Ciba Laboratory, Summit, N.J. for the supplies of hydralazine and chlorisondamine used in this study.

TABLE 1.—EFFECT OF THE ADDITION OF HYDRALAZINE ON THE BLOOD PRESSURE PATIENTS WITH

Patient	*Standing Blood Pressure (mm.Hg)**							*Recumbent Increase in*					
	Control period†	*First month*	*Second month*	*Third month*	*Fourth month*	*Fifth month*	*Sixth month*	*Control period†*		*First month*		*Second month*	
			chlorisondamine-hydralazine									*chlorisondamine-*	
								S	*D*	*S*	*D*	*S*	*D*
AM	168/120	151/100	147/96	147/93	146/98	150/98	151/98	35	11	24	15	23	10
(MC)	161/99	159/92	162/94	158/90	156/89	161/88	162/87	43	10	27	12	25	12
GG	153/110	148/102	157/101	154/103	145/99	145/101	155/105	58	6	41	9	16	7
DB	156/100	162/102	161/98	160/97	161/97	152/96	155/94	23	14	25	5	16	4
Mean	160/107	155/99	157/97	155/96	152/96	152/96	156/96	40	10	29	10	20	8
			mecamylamine-hydralazine									*mecamylamine-*	
(LE)	154/114	145/100	148/100	143/99	132/92	138/93	136/88	58	12	50	19	33	16
CA	155/107	158/111	143/101	133/94	125/89	124/91	119/86	32	7	5	6	10	−1
(JM)	155/93	171/98	176/101	184/106	163/94	149/85	134/77	75	32	53	13	57	22
WP	135/103	119/90	140/99	135/98	139/97	134/94	139/96	69	36	73	41	12	30
(WF)	168/115	172/118	165/108	177/116	148/102	155/108	135/93	33	8	27	6	16	7
MR	147/102	157/97	148/87	152/92	148/89	149/90	147/92	77	33	40	18	36	19
KW	157/91	183/91	146/80	145/77	137/76	136/75	153/80	69	18	26	3	56	5
(ES)	144/92	156/93	162/91	148/89	142/86	152/89	135/91	56	12	17	0	13	0
PW	146/92	159/94	150/88	153/92	151/90	145/88	148/94	33	20	13	14	17	19
Mean	151/101	157/99	153/99	152/96	142/90	142/90	138/88	56	20	34	13	28	13
			mecamylamine-placebo									*mecamylamine-*	
SE	152/113	158/115	144/111	138/102	138/102	139/101	140/102	53	17	37	14	39	13
LJ	158/96	150/92	162/100	179/110	178/107	163/93	151/93	40	19	45	23	38	20
GJ	174/108	171/111	171/111	167/110	163/108	138/93	133/89	57	16	62	14	59	16
LM	180/107	130/86	151/98	154/98	157/104	136/91	146/94	36	14	98	39	82	37
Mean	166/106	152/101	157/105	161/105	159/105	144/95	143/95	47	17	60	23	55	21

S = Systolic D = Diastolic

Initials in parentheses indicate patients who had previously undergone splanchnicectomy.

Each figure represents the average of twice daily blood pressure readings for one month.

*Dose adjusted by patient as necessary to maintain standing systolic BP near 150 mm.Hg.

†Average BP of the last 2 weeks of administration of blocking agents alone after a period of 1 to 12

It will be observed that after about the third month of treatment the requirement of ganglion-blocking was reduced, but that a negligible reduction in the orthostatic diastolic blood pressure gradient was

respond to hydralazine. Failure of such abnormalities to appear makes it unlikely that the occasionally observed hypotensive effects of hydralazine were an early manifestation of the depressor response which is seen commonly in the full-blown lupus erythematosus syndrome (Dustan *et al.*[1], Perry and Schroeder[3]). Five patients underwent a 2-week withdrawal of the hydralazine while the dosage of ganglion-blocking agent was kept constant (Table 2). Two subjects (PW, ES) who had failed to show a rise in blood pressure when the hydralazine was discontinued were the same who had had no decrease in the requirement for ganglion-blocking agent after addition of hydralazine. The 3 patients (CA, LE, and WF) who had reduced the dose of ganglion-blocking agent 54%, 25% and 25% respectively while on hydralazine, showed a rise in blood pressure during the withdrawal period. There is no doubt that in these 3 cases hydralazine had an added hypotensive action.

Table 3 illustrates the effect of the additional use of chlorothiazide* in

*We are indebted to Dr. John Beem, Merck Sharp and Dohme for the supplies of chlorothiazide and mecamylamine used in this study.

READINGS AND DOSE REQUIREMENTS OF GANGLION-BLOCKING AGENTS IN SEVERE HYPERTENSION

*Blood Pressure (mm.Hg)**								*Blocking Agent: Daily Dose (mg.)**						
Third month		*Fourth month*		*Fifth month*		*Sixth month*		*Control period†*	*First month*	*Second month*	*Third month*	*Fourth month*	*Fifth month*	*Sixth month*
hydralazine										*chlorisondamine-hydralazine*				
S	*D*	*S*	*D*	*S*	*D*	*S*	*D*							
17	13	23	13	21	11	16	12	250	230	185	190	150	170	160
27	12	28	11	22	8	17	13	350	350	350	350	250	250	250
14	7	38	14	37	8	29	4	150	150	150	143	130	125	125
13	4	12	4	18	7	16	8	100	150	150	125	125	150	150
18	9	25	11	25	9	20	9	212	220	209	202	164	174	171
hydralazine										*mecamylamine-hydralazine*				
31	15	36	17	34	12	31	16	40	40	40	40	30	20	30
18	5	29	4	28	8	27	8	65	65	60	75	50	35	30
59	23	69	28	68	28	66	28	60	60	60	60	60	60	30
49	39	52	34	58	37	55	38	70	70	70	57	57	45	45
17	7	31	13	30	9	42	19	20	20	20	20	20	20	15
36	17	54	23	49	19	57	22	45	45	45	45	45	45	45
58	14	73	19	74	22	55	14	75	75	75	75	75	75	75
29	6	37	11	35	9	26	9	55	55	55	55	55	55	55
19	15	23	19	19	16	30	14	27.5	35	32	32	29	35	35
35	16	45	19	47	17	43	19	51	52	51	51	47	43	39
placebo										*mecamylamine-placebo*				
40	13	40	13	37	19	30	18	10.5	10	7.5	7.5	7.5	7.5	7.5
26	11	23	11	31	20	43	22	27.5	27.5	25	20	16	19	15
67	17	77	20	99	29	87	32	50	46	47.5	47.5	47.5	47.5	50
77	35	68	26	88	35	79	31	45	45	45	45	45	45	45
53	14	52	18	65	26	61	26	33	35	34	33	32	32	32

months of continuous treatment.
agent was reduced in 6 of 13 patients, that the change in systolic blood pressure on assuming recumbency achieved.

patients being treated with ganglion-blocking drugs. Subjects with prior splanchnicectomy were excluded from this series since it is well known that they exhibit increased sensitivity to chlorothiazide (Weller and Hoobler[7]). The maximum effect appeared after a few days or weeks. In some exceptional cases the greatest hypotensive response was observed after one or 2 months. The reduction in requirement for ganglion-blocking agent averaged 45% but the orthostatic gradient was only slightly reduced. One patient (PW) previously refractory to added hydralazine, experienced a 50% reduction in the requirement for mecamylamine when chlorothiazide was added.

Discussion. Hydralazine, when added to a ganglion-blocking regimen, reduced the requirement for the latter drug in 6 of 13 hypertensive patients studied over a 6-month period. A negligible reduction in the orthostatic blood pressure gradient was seen. None of the subjects became normotensive. These observations diverge from those of Rast and Orgain[5] who claimed a consistent reduction in the requirement for ganglion-blockade and of Perry and Schroeder[4] who claimed furthermore that sustained normoten-

TABLE 2.—EFFECT OF THE ADDITION AND WITHDRAWAL OF HYDRALAZINE ON THE BLOOD PRESSURE READINGS AND DOSE REQUIREMENT OF GANGLION-BLOCKING AGENTS

Patient	*Standing Blood Pressure* (mm.Hg)*			*Increase in Blood Pressure Standing to Recumbent* (mm.Hg)*						*Mecamylamine daily dose (mg.)*		
	Control Period†	*6-Month Treatment†*	*Withdrawal Period*	*Control Period†*		*6-Month Treatment†*		*Withdrawal Period*		*Control Period†*	*6-Month Treatment†*	*Withdrawal Period*
				S	*D*	*S*	*D*	*S*	*D*			
CA	155/107	119/86	148/1 9	32	7	26	8	32	1	65	30	30
LE	154/114	136/88	143/93	58	12	32	15	35	12	40	30	30
WF	168/115	134/92	158/116	33	8	42	20	33	5	20	15	15
ES	144/92	135/90	123/80	56	12	25	9	86	21	55	55	55
PW	146/92	148/93	120/88	33	20	30	15	74	32	27.5	35	35

S = Systolic D = Diastolic

*Each figure represents the average daily blood pressure readings taken during a 2 week period.

†Dose of mecamylamine adjusted by patient as necessary to maintain standing systolic blood pressure near 150 mm.Hg.

Control period represents the last 2 weeks of treatment on mecamylamine alone.

Six month treatment represents the last 2 weeks of period in which hydralazine was added.

Withdrawal period represents the first 2 weeks after hydralazine was discontinued and in which the dose of blocking agent was maintained unchanged. It can be observed that the 3 patients (CA, LE, WF) who had a reduced requirement for blocking agent when hydralazine was added, experienced a rise in blood pressure after the withdrawal of this drug. No effect while on treatment or after withdrawal was seen in the other 2 patients (ES, PW).

TABLE 3.—EFFECT OF THE ADDITION OF CHLOROTHIAZIDE ON THE BLOOD PRESSURE READINGS AND DOSE REQUIREMENTS OF GANGLION-BLOCKING AGENTS

Patient	*Standing Blood Pressure* (mm.Hg)*		*Increase in Blood Pressure Standing to Recumbent* (mm.Hg)*				*Blocking Agent daily dose (mg.)*	
	Control Period	*After Chlorothiazide*	*Control Period*		*After Chlorothiazide*		*Control Period*	*% Reduction after Chlorothiazide*
			S	*D*	*S*	*D*		
GL	150/104	150/100	44	8	20	1	M 30	83
LC	125/88	150/100	64	36	0	4	P 150	83
WF	140/100	118/60	30	12	54	48	M 30	75
SC	186/110	134/90	9	5	12	10	M 60	66
MB	180/95	134/90	20	10	41	0	M 7½	66
ML	130/90	145/90	90	30	55	20	M 45	66
BH	170/110	140/100	20	10	30	10	M 12½	60
PW	145/92	150/90	43	28	30	25	M 35	50
HW	150/100	148/100	25	10	12	8	M 30	50
SD	145/100	145/115	30	6	20	0	M 10	50
GP	178/120	172/108	2	4	10	2	M 10	50
AC	175/105	155/100	20	5	10	0	M 20	25
ME	160/82	165/88	40	30	29	14	M 5	0
JE	220/130	230/118	40	5	1	2	M 7½	0
MD	215/140	140/90	15	0	60	25	M 7½	0
LL	210/118	172/118	1	15	10	2	M 5	0
Mean	167/105	153/98	31	13	25	11		45

S = Systolic D = Diastolic M = Mecamylamine P = Pentolinium

*Each figure represents the average of twice daily blood pressure readings taken during a 2-week period. As in the previous figure, the dose of ganglion-blocking agent was adjusted by the patient to maintain near normal blood pressure in the standing position.

Control period represents the average of the last 2-weeks of treatment on ganglion-blocking agents alone.

After chlorothiazide represents the average of the last 2-weeks of a 6-week period in which this drug was added in a dose of 0.5 gm. twice daily.

It can be observed that the requirement of ganglion-blocking agent after the addition of chlorothiazide was reduced in 12 of the 16 patients and that the orthostatic gradient of systolic and diastolic blood pressure was reduced slightly.

sion was sometimes achieved by prolonged hexamethonium-hydralazine therapy. Their studies differed in that a generally greater dosage of drugs was employed, and that hexamethonium rather than mecamylamine or chlorisondamine was prescribed. Although the period of observation in their study was more prolonged, this does not seem to be a factor in the divergent results since in our experience continued treatment (up to 14 months in one case) did not alter the findings. Although the onset of a hypotensive response to hydralazine did not appear until the third month of treatment, it was not related to any toxic effect detectable by hematologic studies or by an abnormality in serum globulin. Such findings if present, might have suggested the imminence of the lupus erythematosus syndrome, a condition commonly associated with normalization of the blood pressure.

Our experience with the additive use of chlorothiazide on the other hand is very encouraging and conforms with the experiences of others (Freis *et al.*[2], Weller and Hoobler[7]). Not only was the drug well tolerated, but there was a concomitant reduction of 45% in the dose of ganglion-blocking agent.

Our experiments suggest that hydralazine in addition to chlorothiazide might be used to reduce the requirement for ganglion-blocking drugs. An adequate trial of such treatment would require that a dosage of at least 400 mg. of hydralazine daily be maintained for a minimum period of 3 months.

Conclusions. 1. Chlorothiazide (1 gm. daily) or hydralazine (400 mg. daily) may be useful in reducing the dosage of ganglion-blocking drugs required for the treatment of hypertension.

2. This effect is generally achieved within a few weeks after chlorothiazide and during the second 3 months of treatment with hydralazine.

3. No intolerable side effects appeared following the addition of chlorothiazide. Twelve of 16 patients exhibited a reduced dosage requirement for blocking drugs and fewer side effects.

4. Four of 17 patients given hydralazine in addition to ganglion-blocking agents were unable to tolerate the drug because of side effects. Seven did not demonstrate a reduction in the requirement for ganglion-blockade or in orthostatic blood pressure gradient. The remaining 6 experienced substantial benefit.

5. It is concluded that severe hypertension should be treated with chlorothiazide and ganglion-blockade at first. Additional hydralazine given for at least 3 months may further reduce the requirement for ganglion-blocking drugs in some patients.

REFERENCES

1. **Dustan, H. P., Taylor, R. D., Corcoran, A. C.,** and **Page, I. H.:** J. Am. Med. Assn., **154,** 23, 1954.
2. **Freis, E. D., Wanko, A., Wilson, I. M.,** and **Parrish, A. E.:** Ann. New York Acad. Sci., **71,** 450, 1958.
3. **Perry, H. M., Jr.,** and **Schroeder, H. A.:** J. Am. Med. Assn., **154,** 670, 1954.
4. Iidem: Circulation, **13,** 528, 1956.
5. **Rast, C. L., Jr.,** and **Orgain, E. S.:** Ibid., **12,** 361, 1955.
6. **Schroeder, H. A., Morrow, J. D.,** and **Perry, H. M., Jr.:** Ibid., **10,** 321, 1954.
7. **Weller, J. M.,** and **Hoobler, S. W.:** Ann. Int. Med., **50,** 106, 1959.

(Interlingua on page 771)

HYDROCHLOROTHIAZIDE AND ITS EFFECT UPON THE URINE CONTENT OF SODIUM, POTASSIUM AND CHLORIDE*

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The clinical efficacy of hydrochlorothiazide as a diuretic agent is now well known. We have previously reported in this journal our experience with the clinical use of this drug[2]. It is exceedingly well tolerated regardless of the route of administration, orally or intravenously. Toxic effects have not occurred other than infrequent nausea or other types of gastrointestinal upset. Laboratory studies, including hematological surveys, urinalyses, and those for the detection of hepatic derangement, have demonstrated no significant change specifically attributable to the drug. Hyperuricemia is occasionally produced, for unknown reason, particularly in those with pre-existing renal dysfunction, or obvious or latent gout. On the other hand, untoward effects due to dehydration or to electrolyte depletion are not infrequent, and may occur when the drug is used indiscriminately, with restriction of intake of water or electrolytes or both, or if there is an underlying disturbance in electrolyte balance.

In an attempt to understand better the nature of these untoward effects and thereby possibly to prevent their occurrence, a study was made of the effect of various doses of hydrochlorothiazide, given orally or intravenously, upon the urine content of sodium, potassium and chloride.

Method and Material. Urine volume and content of sodium, potassium and chloride were determined in 4 persons following the oral and intravenous administration of various doses of hydrochlorothiazide. These 4 included W.W., a 68-year-old man with coronary artery disease and myocardial infarction, N.A., a 76-year-old man with coronary artery disease and pulmonary emphysema, C.W., a 67-year-old man with essential hypertension and coronary artery disease, and A.B., a 71-year-old man with diabetes mellitus and coronary artery disease. They were admitted to the hospital because of cardiac decompensation and at the time of study were asymptomatic with sinus rhythm and stable weight. For at least one week prior to study, intake of sodium was restricted to 200 mg. daily. On the day of study, a liberal fluid intake was encouraged.

Hydrochlorothiazide† was given at 9:00 A.M. orally on the first day of the study

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and intravenously on the second day in a dose of 200 mg. for the first 2 persons, 50 mg. for the third and 25 mg. for the fourth.

Urine was collected hourly from 8:00 A.M. to 3:00 P.M. after spontaneous voiding. Urine volume was measured in a graduated cylinder. Concentrations of sodium and potassium were determined by an internal standard flame photometer. Concentration of chloride was determined by chemical analysis. Content is the product of urine volume and electrolyte concentration.

To determine the effect of daily administration of the drug upon urine electrolyte content, 2 persons were given 25 mg. of hydrochlorothiazide orally every day for 8 and 7 days respectively. These 2 are H.D., a 54-year-old man, and S.D., a 59-year-old man,

TABLE 1.—URINE VOLUME AND CONTENT OF SODIUM, POTASSIUM AND CHLORIDE FOLLOWING THE ADMINISTRATION OF ORAL AND INTRAVENOUS HYDROCHLOROTHIAZIDE

	Vol. (ml.)	*Na*	*K (mEq.)*	*Cl*	*Vol. (ml.)*	*Na*	*K (mEq.)*	*Cl.*
W.W.			CONTROL					
8– 9 A.M.	120	3.7	4.6	5.8	90	4.5	5.8	8.8
Hydrochlorothiazide	200 mg. orally at 9 A.M.				200 mg. I.V. at 9 A.M.			
9–10 A.M.	180	2.2	3.1	4.7	No specimen			
10–11 A.M.	250	9.7	6.0	15.7	240	12.9	10.1	21.6
11–12 M.	125	10.7	4.6	8.4	270	16.7	14.8	22.1
12– 1 P.M.	100	6.8	4.9	8.3	270	9.4	15.9	17.8
1– 2 P.M.	200	15.0	5.2	13.6	150	5.7	5.1	10.2
2– 3 P.M.	190	11.8	5.3	11.2	180	7.2	6.3	12.4
N.A.			CONTROL					
8– 9 A.M.	145	8.8	5.9	10.6	60	3.4	2.4	6.7
Hydrochlorothiazide	200 mg. orally at 9 A.M.				200 mg. I.V. at 9 A.M.			
9–10 A.M.	80	3.6	2.3	5.3	30	0.9	1.2	2.3
10–11 A.M.	175	9.2	3.8	10.6	60	1.7	3.0	5.8
11–12 M.	220	13.6	6.2	17.4	90	7.9	7.0	18.7
12– 1 P.M.	80	4.9	3.2	7.2	60	2.2	2.2	4.9
1– 2 P.M.	300	18.6	8.1	21.0	180	6.3	5.7	7.9
2– 3 P.M.	210	13.4	5.9	15.7	150	6.3	5.7	9.9
C.W.			CONTROL					
8– 9 A.M.	30	2.8	2.7	3.7	60	4.6	3.3	3.6
Hydrochlorothiazide	50 mg. orally at 9 A.M.				50 mg. I.V. at 9 A.M.			
9–10 A.M.	60	4.8	4.2	4.7	100	7.3	6.2	7.9
10–11 A.M.	No specimen				125	9.1	3.5	7.6
11–12 M.	60	3.8	3.3	4.2	No specimen			
12– 1 P.M.	150	12.0	17.8	13.1	100	6.8	4.6	6.6
1– 2 P.M.	No specimen				75	4.4	5.5	5.8
2– 3 P.M.	No specimen				115	7.9	5.8	7.6
A.B.			CONTROL					
8– 9 A.M.	60	1.5	11.4	3.6	120	5.5	4.2	5.4
Hydrochlorothiazide	25 mg. orally at 9 A.M.				25 mg. I.V. at 9 A.M.			
9–10 A.M.	No specimen				240	10.8	20.4	18.5
10–11 A.M.	90	1.6	8.1	6.4	120	10.8	11.8	14.9
11–12 M.	No specimen				60	4.5	8.5	9.5
12– 1 P.M.	180	4.7	14.4	27.0	150	6.9	12.3	14.4
1– 2 P.M.	240	4.8	19.2	25.2	210	4.6	12.6	15.3
2– 3 P.M.	No specimen				150	5.8	10.8	11.4

both with coronary artery disease and myocardial infarction. Daily intake of sodium was restricted to 400 mg. in H.D. and 200 mg. in S.D.

Results. Urine volume and content of electrolytes after oral and intravenous administration of hydrochlorothiazide are given in Table 1.

Following oral or intravenous administration of hydrochlorothiazide, urine volume increases within one or 2 hours, reaches a peak during the second to fifth hour and remains increased during the sixth hour. The increase tends to appear earlier and to be greater after a dose of 200 mg. than after 25 mg.

Sodium content increases usually in one hour, reaches a peak in 2 to 5 hours and remains increased during the sixth hour. The increase in sodium content tends to appear earlier after intravenous than oral administration of hydrochlorothiazide. The maximal hourly content is two to four times that of the control regardless of route of administration.

Potassium content increases in one to 5 hours. The increase is approximately 1.5 times that of the control except after intravenous administration or after small doses when the increase may be as much as nearly five times that of the control. Potassium content was greater than that of sodium in only 5 of 18 determinations following hydrochlorothiazide given orally and in 10 of 22 determinations following hydrochlorothiazide given intravenously. Moreover, the content of potassium always exceeded that of sodium in the one given 25 mg. hydrochlorothiazide orally or intravenously.

Chloride content tends to parallel that of sodium. In only 7 of 40 determinations was the chloride content less than that of sodium, the decrease varying from 0.1 to 2.3 mEq., whereas in 33, it exceeded the sodium content by an amount varying from 0.4 to 22.3 mEq., the increase averaging 5.2 mEq. In only three instances was the chloride content less than that of potassium. In these three, the content of potassium was also greater than that of sodium. The chloride content exceeded the sum of the contents of sodium and potassium in 6 instances only. Three of these had relatively small electrolyte contents and 2 had large contents of potassium which exceeded that of the sodium which was small.

The daily urine volume and content of electrolytes following the daily oral

TABLE 2.—DAILY URINE VOLUME AND CONTENT OF SODIUM, POTASSIUM AND CHLORIDE FOLLOWING DAILY ORAL ADMINISTRATION OF 25 MG. HYDROCHLOROTHIAZIDE

	Subject: H.D.				*Subject: S.D.*			
	Vol. (ml.)	*Na*	*K (mEq.)*	*Cl*	*Vol. (ml.)*	*Na*	*K (mEq.)*	*Cl*
Control day	2320	14 7	71 9	+	1560	7 5	32 4	0 0
Day 1	2220	75 5	88 8	51 1	1880	6 8	80 8	73 3
Day 2	1360	44 4	34 4	33 7	1720	60 3	62 4	49 0
Day 3	1775	49 3	62 1	36 4	1580	32 4	47 4	25 0
Day 4	—	—	—	—	2006	35 4	54 0	24 0
Day 5	—	—	—	—	1960	27 7	62 7	29 0
Day 6	—	—	—	—	2560	77 6	80 6	65 1
Day 7	—	—	—	—	2008	55 8	50 0	42 6
Day 8	1060	19 6	35 0	17 8	—	—	—	—

administration of 25 mg. hydrochlorothiazide are given in Table 2.

The urine volume was variable. In one, the urine volume always exceeded the control and in the other, it was always less than the control.

Sodium content was almost always increased, the increase being as much as five times that of the control in one and 10 times in the other. In the latter, it remained substantially increased for 7 days and in the former it tended to approach the control value on the eighth day. Potassium content was greater than the control in only one of 4 determinations following hydrochlorothiazide in H.D. and in all of the 7 determinations in S.D. In the latter, the increase was as much as 2.5 times that of the control. The content of potassium exceeded that of sodium in 9 of 11 determinations. Chloride content was also increased and the increase exceeded that of sodium or of potassium. However, the absolute values for chloride content were smaller than that of sodium or of potassium in all but two. These two had lower sodium contents.

Discussion. A major concern of treatment with hydrochlorothiazide is electrolyte depletion. The administration of hydrochlorothiazide results mainly in an increased urinary excretion of chloride, sodium and potassium, regardless of an increase in urine volume.

In the absence of an increase in extracellular water, urine volume may not increase after hydrochlorothiazide. Indeed, in a person with edema due to cardiac decompensation, continued daily use of hydrochlorothiazide results in diuresis with weight loss until a so-called "dry" stable weight is obtained. If hydrochlorothiazide administration is then continued, urine volume may increase slightly if at all and weight remains constant. The person taking hydrochlorothiazide is usually aware of this change in urinary response.

Urine volume increase, when present, usually occurs within one hour following administration of hydrochlorothiazide and persists for at least 6 hours. The increase tends to be greater earlier following intravenous administration of the drug. Also, a large dose produces an early effect which tends to be sustained and even increased with time whereas a small dose produces mainly a delayed effect.

Regardless of the increase in urine volume, the urine content of chloride, sodium and potassium increases, and chloride is the dominant ion. The amount of chloride present is usually less than the sum of sodium and potassium, the discrepancy being made up, at least in part, probably by the excretion of bicarbonate which renders the urine alkaline. Large urinary contents of chloride sufficient to exceed the combined amounts of sodium and potassium may occur when the urine contains a disproportionately large amount of potassium. Indeed, with continued administration of the drug, potassium may become the major ion excreted.

Ordinarily, the major cation excreted is sodium. Urine sodium content increases usually in one hour, reaches a peak in 2 to 5 hours, and remains increased during the sixth hour. In those with stable weight and severely restricted intake of sodium, the maximal hourly increase of urine sodium content is 2 to 4 times that of the control. Obviously, under such circumstances, the resultant negative sodium balance readily produces depletion of sodium from the body which becomes increasingly severe if uncorrected. Such depletion may be prevented or at least lessened both by the administration of adquate sodium and by the ces-

sation of continuous use of hydrochlorothiazide as quickly as possible. It has been our policy to encourage in persons who receive hydrochlorothiazide daily a diet which is unrestricted in salt, except for the use of a salt shaker. Sodium restricted diets are used only infrequently and then only under special circumstances. Moreover, a daily dose of hydrochlorothiazide is administered only after the response to the previous day's dose is determined. In the absence of symptoms attributable to dehydration or to electrolyte depletion, or of a weight loss greater than 3 pounds, hydrochlorothiazide is administered daily until a "dry" stable weight is established and then is given intermittently depending upon need and response. The lessons learned from the use of mercurial diuretics should not be forgotten (Vogl[1]).

The daily dose of hydrochlorothiazide which we employ is 200 mg. Additional amounts do not produce increased urine volume. It is given either in one dose or preferably in two divided doses to minimize the occasional occurrence of gastrointestinal side effects. The second dose is given not later than 3:00 P.M. to avoid interference with nocturnal rest by diuresis.

Large doses when given orally produce mainly an increase in urinary content of sodium and chloride and relatively little increase in potassium. A greater increase in potassium content appears after intravenous use. It is for this reason and also because of the dangers inherent in any medication given intravenously that the oral route is preferred.

Greatly increased urine contents of potassium may also occur following the administration of small doses of hydrochlorothiazide, intermittently or continuously. Indeed, after 25 mg. the amount of potassium may be as much as 5 times that of the control whereas, after 200 mg., it may not exceed 1.5 times that of the control. Moreover, with continued administration of the drug, there may be a preferential excretion of potassium. The reason for these differences in response is unknown. Nevertheless, it suggests that potassium depletion is more likely to occur following small rather than large doses of hydrochlorothiazide and also during continuous administration rather than intermittent administration. It is for these reasons that potassium supplementation is usually unnecessary with unrestricted diets and with intermittent therapy. Conversely potassium supplementation should be seriously considered if intake is restricted or if the drug is given continuously, and particularly in small amounts or in those with inherent predisposition to potassium loss.

To decrease and perhaps prevent significant potassium depletion, a capsule of hydrochlorothiazide containing 7.7 mEq. of potassium has been made available to us for clinical trial. It contains either 25 or 50 mg. hydrochlorothiazide. This preparation is generally well tolerated. Occasionally, gastrointestinal upset manifested by nausea, abdominal pain or diarrhea occurs because of the added potassium. Four such capsules provide 30.8 mEq. of potassium, obviously decreasing the degree and frequency of potassium depletion. Nevertheless, it must be emphasized that the amount of potassium which may be lost in any given instance is clinically unpredictable. Indeed, identical doses of hydrochlorothiazide may produce dissimilar effects on urine electrolyte content in the same individual under different circumstances. Finally, we have also observed that continued use of the drug, and for a long time, does not necessarily produce depletion of potassium, in the absence of dietary restriction or urinary loss due to intrinsic dysfunction.

Summary and Conclusions. 1. Urine

volume and content of sodium, potassium and chloride were determined in 4 persons with stabilized cardiac disease and controlled sodium intake before and after the oral and intravenous administration of hydrochlorothiazide.

2. Hydrochlorothiazide produced an increased urine volume and content of sodium, potassium and chloride which persisted for at least 6 hours. The urine volume increased earlier and was greater following intravenous than oral use of the drug.

3. The increase in chloride usually exceeded that of sodium or potassium and was less than the sum of both.

4. Potassium content may be relatively little increased after large oral doses compared with that following intravenous or small oral doses. Indeed, potassium may become the dominant ion excreted with continued use of even small doses.

5. Experience with a new preparation of hydrochlorothiazide containing potassium is described.

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REFERENCES

1. **Vogl, A.:** Diuretic Therapy. Baltimore: Williams & Wilkins Co., 1953.
2. **Zatuchni, J., King, W.,** and **Resinski, M.:** Am. J. Med. Sci., **237**, 479, 1959.

SUMMARIO IN INTERLINGUA

Hydrochlorothiazido e Su Effecto Super le Contento Urinari de Natrium, Kalium, e Chloruro

1. Le volumine de urina e le contento urinari de natrium, kalium, e chloruro esseva determinate in quatro subjectos con stabilisate morbo cardiac, post regulation del ingestion de natrium e ante e post le administration oral e intravenose de hydrochlorothiazido.

2. Hydrochlorothiazido produceva un augmento del volumine de urina e del contento urinari de natrium, kalium, e chloruro. Le effecto del agente persisteva durante al minus 6 horas. Le augmento del volumine de urina esseva plus marcate e plus rapide post le administration intravenose que post le administration oral del droga.

3. Le augmento de chloruro excedeva usualmente le augmento de natrium e etiam le augmento de kalium. Illo no excedeva le summa del duo.

4. Le augmento del contento urinari de kalium post grande doses oral de hydrochlorothiazido pote esser relativemente micre in comparation con le augmento que occurre post doses intravenose o post micre doses oral del agente. Con le continue uso de solmente micre doses de hydrochlorothiazido, kalium pote provar se le ion dominante in le excretion.

5. Es describite experientias con un nove preparato de hydrochlorothiazido que contine kalium.

METASTATIC CARCINOMA IN THE CIRRHOTIC LIVER

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Hepatic metastases are rarely found in the cirrhotic patient. It is surprising to note that only 25 cases of metastatic carcinoma in the cirrhotic liver were reported. These included 2 cases of biliary cirrhosis with metastatic lesions (Achard and Laubry[1], Colwell[2], Hanot and Gilbert[3], Lieber[4], Lisa, Solomon and Gordon[5], Rabl[6], Torres[8], Wallach, Hyman and Angrist[9]).

Recently, we encountered 3 cirrhotic patients with extrahepatic carcinoma and hepatic metastases. The rarity of this condition justifies the following report.

Case Reports. case 1. *Clinical History.* A 47-year-old white man was admitted to the VA West Side Hospital, Medical Service on June 25, 1957, and death occurred on August 9, 1957. He complained of 60 pounds weight loss in the last year and progressive weakness in the last month before admission. During the past 10 years he had been drinking a fifth of whiskey daily and during the last year his meals had not been adequate.

Physical Examination. On admission, the patient was a poorly developed undernourished, dehydrated and cachectic white male. The blood pressure was 88/40 mm. Hg; the pulse rate was regular and 128 a minute; the temperature was 97° F. and the weight 106 lbs. Clubbing of the fingers and toes was noted. The respiratory and cardiovascular systems were negative. The liver was palpable 12 cm. below the right costal margin in the midclavicular line. It was firm, nontender and had a smooth surface. Bowel sounds were hyperactive. Increased pigmentation of the posterior cervical area was noted. There were no spider nevi of the skin. There was no icterus.

Laboratory and Special Examinations. On admission, the hemoglobin was 10 gm.; hematocrit 37% with a sedimentation rate of 32 mm. per 1 hour; white blood cell count was 8400 per c.mm. with 62% lymphocytes, 36% neutrophils and 2% monocytes. On August 8, 1957, the white blood cell count was 13,000 with 68% neutrophils and 32% lymphocytes. On July 24, 1957, the reticulocyte count was 2.2% and the 2-hour Watson test was 0.7 EU. On July 1, 1957, the bleeding time was 1 min. 30 sec.; Lee-White coagulation time was 7 min. 15 sec.; and a prothrombin time was 13 sec. with a control of 13 sec. On admission, the nonprotein nitrogen was 74 mg. per 100 ml.; total bilirubin 0.7 mg. per 100 ml. and direct 0.3 mg. per 100 ml.; Bromsulphalein retention 13%; thymol turbidity 1.4 units; cephalin flocculation was negative; alkaline phosphatase 8 Bodansky units; serum sodium 140 mg. per 100 ml.; serum potassium 4.3 mg. per 100 ml.; serum chlorides 90 mg. per 100 ml.; CO_2-combining power 21.4 mEq. per liter; lactic dehydrogenase of serum 187 units; glutamic oxalic acid transaminase of serum 13 units; glutamic pyruvic acid transaminase of serum 41 units.

On August 8, 1957, serum total protein was 5 gm. per 100 ml. with albumin 3 gm.

per 100 ml. and globulin 2 gm. per 100 ml. Stools for occult blood were 2 plus positive on one occasion and 1 plus positive on two occasions. Bone marrow aspiration on July 2, 1957, revealed granulocytic bone marrow with left shift, giant bands and increased number of plasma cells. Liver biopsy on July 9, 1957, revealed fatty cirrhosis with focal necrosis. Roentgenographic examination with barium enema of the large bowel on July 11, 1957, revealed a deformity of the cecum suggesting an extrinsic or intrinsic neoplastic lesion.

Course in Hospital. The patient's hospital course lasted 46 days and was characterized by anorexia, diarrhea and anemia. On the 23rd hospital day the hemoglobin dropped to 8.5 gm. and he was given 2 units of blood. At the same time the patient developed right lower quadrant pain and abdominal distention. Roentgenographic examination of the abdomen revealed intestinal obstruction. On the 39th hospital day the temperature rose to 101.5° rectally. On the 45th hospital day, the patient vomited blood and 3 units of blood were given. The patient went into shock and expired soon afterwards.

Necropsy. The body was that of a poorly developed and poorly nourished white male weighing 103 lbs. and measuring 5 ft. 8 in. (170 cm.) in length.

Internal Gross Examination. The peritoneal cavity contained about 100 ml. of purulent fluid. The peritoneal surfaces were covered by fibrinous exudate. A well walled-off perityphlitic abscess was present. This had a direct communication by a sinus tract with a perforated carcinoma of the cecum. This was ulcerating, annular and extended from the ileocecal valve into the base of the appendix vermiformis. The small bowel mucosa was covered by a pseudomembranous exudate. The lumen of the stomach contained about 200 ml. of dark bloody fluid. A moderate number of varicose veins were seen in the lower third of the esophagus. The cirrhotic liver weighed 2400 gm. The surface of the liver was light yellowish tan, smooth and at one level an umbilicated metastatic carcinoma nodule was seen. On surfaces made by cutting, the liver was yellow with obscured normal pattern and areas of pseudolobularity. There were also multiple metastatic carcinoma nodules. The peripancreatic, biliary and ileocecal lymph nodes showed similar metastatic carcinoma.

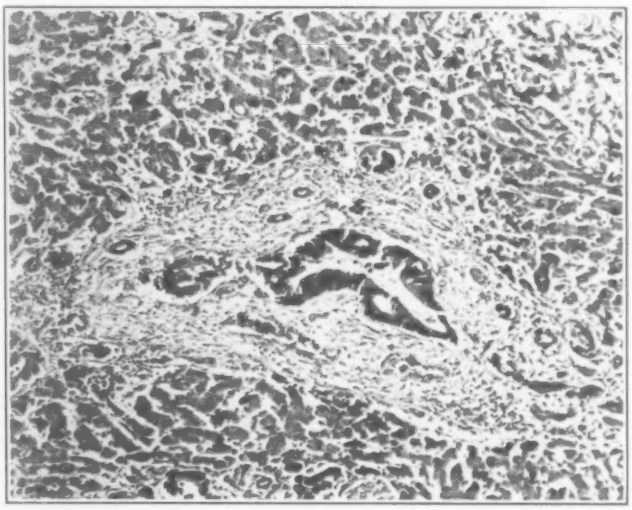

Fig. 1.—1 × 250 showing vascular invasion by adenocarcinoma.

The remaining organs, except for a bronchopneumonia of the right lower lobe of the lungs, diffuse atrophy of the testes and fibrosis of the spleen, were not remarkable.

Microscopic Examination. Microscopic sections of cecum showed mucus-producing adenocarcinoma tissues infiltrating the submucosa, muscularis and serosa. The liver showed replacement of normal lobular architecture by pseudolobules with liver cells con-

taining a moderate amount of large droplet fat, narrow fibrous tissue septa and moderate number of proliferating bile ducts. There also was focal infiltration by mucus-producing adenocarcinomatous tissues with invasion of small sized vessels (Fig. 1). The lymph nodes showed similar metastatic mucus-producing adenocarcinoma.

PATHOLOGICAL DIAGNOSIS. Mucus-producing, perforating adenocarcinoma of the cecum with acute diffuse peritonitis and perityphlitic abscess. Metastatic carcinoma of cirrhotic liver and lymph nodes. Fibrosis of the spleen. Diffuse atrophy of testes. Acute pseudomembranous enteritis (postmortem cultures showed Friedlaender's b.). Bacteremia (postmortem cultures showed Friedlaender's b.). Bronchopneumonia.

CASE 2.—CLINICAL HISTORY. A 61-year-old white man was admitted to the VA West Side Hospital, Medical Service, for the second time on July 12, 1957, and death occurred on July 17, 1957. He was recently discharged from this hospital following a surgical ileotransverse ileostomy for nonresectable carcinoma of the cecum. On second admission, he complained of weakness, weight loss (approximately 20 lbs. within the past 4 months), diarrhea and epistaxis. The patient had a history of alcoholic intake.

Physical Examination. On admission, the patient was well developed and obese. The blood pressure was 140/80 mm. Hg and the pulse rate was regular and 86 per minute. A tumor mass was palpable in the right quadrant of the abdomen and a shifting dullness and fluid wave were noticed. Rectal examination revealed a rectal shelf palpable about 3 in. above the anus and dark stool. The lower extremities were edematous.

Laboratory and Special Examinations. On admission, the hemoglobin was 8.5 gm.; hematocrit 30%; white blood cell count 6650 per c.mm. with 82% neutrophils, 16% lymphocytes, 1% monocytes and 1% basophils; coagulation time 5 minutes, 37 seconds; bleeding time 1 minute; prothrombin time 16 seconds with a control of 13 seconds; blood serum alkaline phosphatase was 17 Bodansky units and cephalin flocculation was 3 plus after 48 hours.

Course in Hospital. The patient's hospital course lasted 5 days. He deteriorated rapidly, developed coma and expired.

Necropsy. The body was that of a well developed, obese and jaundiced white male weighing 176 lbs. and measuring 5 ft. 5 in. (162 cm.) in length.

INTERNAL GROSS EXAMINATION. The peritoneal cavity contained about 3000 ml. of clear yellow fluid. Numerous fibrous adhesions of the peritoneal cavity were present in the region of the ileotransverse colostomy. A stenosing and ulcerating carcinoma was found in the cecum with direct extension into the appendix vermiformis. The small intestines were distended. The varicose veins of the esophagus were moderately prominent. The liver weighed 3000 gm. It was firm on palpation and the nodular, grayish tan surface showed indistinct pale gray nodules of metastatic carcinoma slightly elevated above the surface of the liver with focal areas of hemorrhages. Similar metastatic carcinoma tissues were seen on the cut surface of the liver. The spleen was markedly enlarged weighing 1000 gm. and cut surface was meaty and hyperemic. The urinary bladder, prostate and mesenteric lymph nodes showed metastatic adenocarcinoma. The lower lobe of the lungs showed bronchopneumonia.

MICROSCOPIC EXAMINATION. Microscopic sections of cecum showed highly undifferentiated mucus-producing adenocarcinoma. The liver showed pseudolobules with slight fatty metamorphosis of the liver cells and infiltration by cords of cancerous cells. The latter were found invading the sinusoids (Fig. 2) and small sized veins of the liver, mesenteric lymph nodes, adrenals, gallbladder, urinary bladder and prostate. The right lower lobe of the lungs showed bronchopneumonia.

PATHOLOGICAL DIAGNOSIS. Highly undifferentiated mucus-producing adenocarcinoma of cecum with metastases of cirrhotic liver, gallbladder, urinary bladder, prostate and mesenteric lymph nodes. Cirrhosis of the liver, Laennec's type. Bronchopneumonia.

CASE 3. Clinical History. A 46-year-old white male patient had a resection of the sigmoid colon for an adenocarcinoma with colostomy. At the time of surgery, metastatic nodules were noted on the liver. On November 13, 1958, about 11 months after the original surgery, the patient was readmitted. He was irrational and the history obtained from his wife stated that he had passed bright red blood with his bowel movement. The patient was a chronic alcoholic.

Physical Examination revealed a disoriented chronically ill white male. A functioning sigmoid colostomy was present in the left lower abdomen. The liver edge was palpable 3 finger breadths below the right costal margin.

Laboratory Data. On admission, the hemoglobin was 7.5 gm. with a hematocrit of 27%. White cell count was 16,400 per c.mm. with 86 neutrophils, 5 lymphocytes, 5 mono-

cytes, 2 eosinophils, 1 basophil and 1 band. Urinalysis, on admission, was essentially negative. The blood urea nitrogen was 19 mg. per 100 ml., alkaline phosphatase 8.4 Bodansky units, total protein 6 gm. with a globulin of 3.2 gm.

Course in Hospital. His hospital course was gradually downhill and he died on December 19, 1958, one year after the original operation.

Necropsy. The body was that of a well developed white male weighing 180 lbs. and measuring 5 ft. 9 in. (172 cm.). There was a left colostomy.

INTERNAL GROSS EXAMINATION. The peritoneal cavity contained 5000 ml. of clear fluid. The liver weighed 1700 gm. The organ was hard, firm and grayish tan. There was a large, geographically outlined, flat depressed scar on the outer surface of the right liver lobe. On cut surface, 3 metastatic nodules were seen, each measuring 2 cm. in diameter. The remaining cut surface of the liver showed no definite obliteration of the normal pattern. The esophagus showed prominent varicose veins in its distal third. The large intestine showed the previously described colostomy. The rectum showed a large ulcerating carcinoma. The right upper lobe of the lungs showed an area of infarction. Both pulmonary arteries were filled with large antemortem blood clots. The right heart showed dilatation.

MICROSCOPIC EXAMINATION. Microscopic sections of liver showed broad areas of fibrosis. The liver architecture was considerably disrupted. There were large areas of necrosis of the liver tissue with stromal collapse. Extensive invasion of metastatic adenocarcinoma was seen. The rectal tumor showed adenocarcinoma. The lungs showed areas of infarct and pneumonic exudation.

PATHOLOGIC DIAGNOSIS. Recurrent adenocarcinoma of the rectum. Metastatic carcinoma of liver. Postnecrotic cirrhosis. Multiple pulmonary emboli with infarct of right lung. Bronchopneumonia.

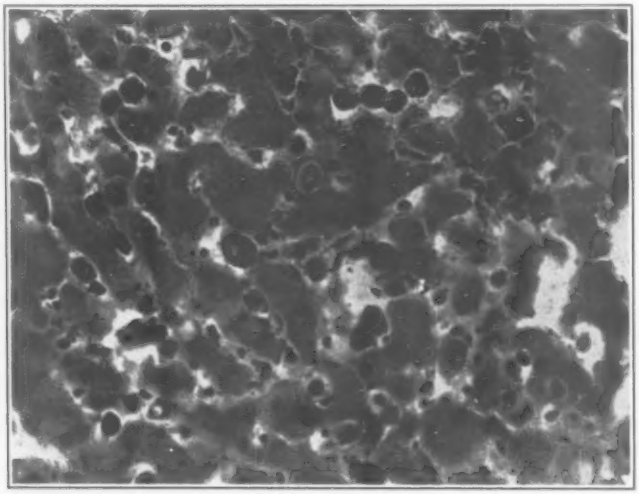

Fig. 2.—1 × 400 showing sinusoidal infiltration by carcinoma.

COMMENT. The remarkably infrequent coincidence of metastatic hepatic carcinoma and cirrhosis of the liver is a phenomenon still unexplained. The liver is quite prominently (28% to 36%) involved in metastatic malignant disease (Lieber[4], Willis[10]). The cirrhotic liver is often (3.41%) the site where primary carcinoma of the liver develops (Stewart[7]). However, primary carcinoma of the liver is found only rarely (0.052%) in the noncirrhotic liver (Stewart[7]). The cirrhotic liver is only infrequently (0.6%) the seat of metastatic carcinoma.

What are the types of cirrhosis to be included in a study of this rare combination of two disease features?

Lieber[4] accepted all cases of every degree of cirrhosis in his series of metastatic carcinoma of the liver with the exception of biliary, syphilitic, and cardiac cirrhosis and cirrhosis associated with tuberculous or parasitic lesions. Wallach, Hyman and Angrist[9] also did not include their cases of biliary cirrhosis with hepatic metastases because of the impossibility of ruling out the development of hepatic metastases prior to the development of biliary cirrhosis.

Our case 3 shows that a similar problem may arise in cases of postnecrotic cirrhosis. At laparotomy, performed one year prior to death, the surgeon noticed the presence of hepatic metastases. The patient received a number of blood transfusions during surgery, therefore, it is possible that the postnecrotic cirrhosis was the result of a serum hepatitis and may have developed in a liver already the seat of metastatic carcinoma.

The small number of reported metastatic hepatic carcinomas in cirrhosis becomes apparent if contrasted with the total number of necropsies performed (Table 1).

TABLE 1

	Necropsies	*Metastasis and Cirrhosis*
Lisa, Solomon and Gordon[5]	6,036	4
Torres[8]	6,356	2
Wallach, Hyman and Angrist[9]	10,156	3
Lieber[4]	29,779	6
	52,327	15

In 52,327 necropsies, only 15 cases of secondary liver carcinoma were found in patients with cirrhosis of the liver. The small number of such cases becomes even more striking if compared with the number of malignancies in the different reports (Table 2).

TABLE 2

	Malignancies	*Hepatic Metastasis in Cirrhosis*
Colwell[2]	2,634	2
Lisa, Solomon and Gordon[5]	782	4
Lieber[4]	5,092	6
	8,508	12

In 8,508 necropsies of malignant lesions only 12 patients displayed hepatic metastases and cirrhosis of the liver. The actual rarity of this combined occurrence can be realized only if compared with the total number of necropsies on cirrhotic patients (Table 3).

TABLE 3

	Cirrhosis	*Hepatic Metastasis*
Wallach, Hyman and Angrist[9]	395	3
Lieber[4]	1,073	6
	1,468	9

In 1,468 cases of cirrhosis, only 9 cases (0.6%) of metastatic liver carcinoma were encountered. This contrasts with 4.9% of hepatic metastases recorded in the general necropsy population (Lieber[4]).

The number of hepatic metastases found in patients with extrahepatic primary carcinoma and cirrhosis illustrated another important aspect of the problem at hand (Table 4).

In 249 cases of extrahepatic malignancy and cirrhosis, 15 patients (6%) with hepatic metastases were found. Willis[10] noted 180 (36%) metastatic

liver carcinomas in a group of 500 consecutive necropsies of malignant diseases. Lieber[4] found 28.6% of metastatic hepatic lesions in his group of carcinomas. This low ratio of hepatic metastases in patients with cirrhosis of

TABLE 4

	Extrahepatic Cancer and Cirrhosis	*Hepatic Metastasis*
Wallach, Hyman and Angrist[9]	67	3
Lieber[4]	133	6
Colwell[2]	27	2
Lisa, Solomon and Gordon[5]	22	4
	249	15

the liver and primary extrahepatic carcinoma eliminates, at least in part, one of the reasons given for the rarity of the combined lesions, namely; that cirrhosis of the liver occurs only rarely in patients with carcinoma of other organs (Lisa, Solomon and Gordon[5]). The figure of only 6% of hepatic metastases in patients with cirrhosis is far below expectations if compared with larger groups of patients with malignant diseases without cirrhosis (Lieber[4], Willis[10]).

Among the causes also quoted for the rarity of hepatic metastases in cirrhosis are the alterations of vascular relationship with production of an internal portal caval shunt with bypass of the liver cells (Lieber[4]). In view of this, the location of the primary tumors and their relation to the portal drainage are of considerable importance. An analysis of the reported cases including our own may elucidate this point (Table 5).

The portal system drains the lower end of the esophagus, the gastrointestinal tract with the exception of the anus, the gallbladder, bile ducts, pancreas and spleen (Lieber[4]).

At least 13 of the 25 cases (52%) were drained by the portal vein. The 5 cases of carcinoma of the esophagus were not included since the reports in the literature did not indicate the location of the malignancy in the esophagus. The figure of 52% compares well with the series reported by Willis[10]. Eighty-eight of his 180 (48%) cases of hepatic metastases could be traced to primary lesions drained by the portal vein (again excluding the carcinomas of the esophagus). The similarity of the ratio in both groups throws some doubt on the validity of the explanation that the internal portal caval shunt in cirrhosis with bypass of the liver cells plays an important part in the rarity of the combined lesions.

TABLE 5

Carcinoma of stomach	6	
" " cecum and ascending colon	4*	
" " sigmoid colon	1	13 cases drained
" " papilla of Vater	1	by portal vein
" " pancreas	1	
" " esophagus	5	
" " breast	3	
" " uterus	1	
" " prostate	1	
" " orbit	1	
" " tongue	1	

*Case 3 of our series was not included.

Wallach, Hyman and Angrist[9] feel that in cirrhosis the duration of life may be too short for metastases to develop. However, this explanation appears insufficient since there is nothing in the literature to indicate that metastases to other organs but the liver are reduced to any striking degree.

Lieber[4] suggests that the fibrosis and subsequent distortion of the small vessels in the liver constitute a mechani-

cal impediment to the spread of the cancerous tissue. Rabl[6] had stated earlier that the thickening of the fibrous tissue and the narrowing of the lymphatics are responsible for the conspicuously low number of hepatic metastases in cirrhosis.

Lisa, Solomon and Gordon[5] offer the opinion that the cirrhotic liver is not a favorable soil for the transplanted tumor cells. In this connection, it may be useful to point out that primary carcinoma of the liver and hepatic metastases show an inverse ratio in cirrhotic patients. It is possible that this inverse ratio indicates a pathophysiologic behavior pattern; namely that cirrhosis, also called a precancerous condition (Stewart[7]), is immune to the tumor cells of the primary extrahepatic carcinomas.

Summary. The rarity of co-existing hepatic metastases and cirrhosis is discussed. Twenty-five cases of this combination are recorded in the literature. Three cases of our own are added to the small series published.

Some authors hesitate to include biliary cirrhosis and metastatic hepatic carcinoma in a report of this combination. They feel that it is impossible to rule out the development of hepatic metastases prior to the development of biliary cirrhosis. One of our cases shows that a similar problem may exist in postnecrotic cirrhosis.

The probable causes for the rarity of the combined condition as defined by the different authors, are evaluated. It is curious to note that primary carcinoma of the liver and hepatic metastases show an inverse ratio. However, it is felt that the extreme rarity of coincident metastatic hepatic carcinoma and cirrhosis is a phenomenon still unexplained.

REFERENCES

1. **Achard, C., and Laubry, C.:** Bull. et mem. Soc. med. d. hop. de Paris, **19**, 335, 1902.
2. **Colwell, H.:** Arch. Middlesex Hosp., London, **5**, 123, 1905.
3. **Hanot, V., and Gilbert, A.:** Etudes sur les Maladies du Foie. Paris: Asselin & Houzeau, 1888.
4. **Lieber, M. M.:** Am. J. Med. Sci., **233**, 145, 1957.
5. **Lisa, J. R., Solomon, C., and Gordon, E. J.:** Am. J. Path., **18**, 137, 1942.
6. **Rabl, R.:** Klin. Wchnschr., **15**, 1681, 1936.
7. **Stewart, M. J.:** Lancet, **2**, 565, 617, 669, 1931.
8. **Torres, E. T.:** Rev. Brasil. Gastroenter., **3**, 395, 1951.
9. **Wallach, J. B., Hyman, W., and Angrist, A. A.:** Am. J. Clin. Path., **23**, 989, 1953.
10. **Willis, R. A.:** Pathology of Tumors. St. Louis: C. V. Mosby, Co., 1953.

(Interlingua on page 739)

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NEONATAL MORTALITY WITH SPECIAL REFERENCE TO INFECTIOUS CAUSES OF DEATH

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IT has been stated by Clifford[6,8] that the neonatal mortality rate in the United States at present is approximately 19 to 20 per 1000 live births and that application of existing knowledge and techniques could reduce this to 14 per 1000 live births, a saving of 20,000 plus babies per year in the United States alone. He, as well as many others, feels that the most important single cause of disease and death in newborn infants is asphyxia. Because of the many physiologic changes such as high CO_2, low pH, high lactic acid levels, vascular damage with edema, petechial hemorrhages throughout the body, thromboses and resultant tissue degeneration produced by asphyxia, symptoms referable to the central nervous system may be manifest at or shortly after birth, for example, bulging fontanelle, separated sutures, convulsions, apnea, irregular respirations. The effect of asphyxia upon the brain centers is reflected in acceleration of the fetal heart, aspiration *in utero*, difficulty in newborn resuscitation, and hypertonia or hypotonia.

Asphyxia confined to the intrauterine period may not be fatal if proper respiratory mechanisms are present at birth. However, if the respiratory center has been embarrassed or pulmonary complications are present, further anoxemia may occur and the patient's

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condition will grow worse. Damage to the respiratory center may produce ineffectual respiratory effort with weak cry and incompletely expanded lungs with multiple areas of atelectasis. If the infant continues to live, edema develops and an increased susceptibility for the development of pneumonia is noted.

Asphyxia probably also plays a large part in the production of lethal hemorrhage. MacGregor[15] has stated that asphyxia produces severe venous engorgement which may result in severe pulmonary hemorrhage. This can well be applied to hemorrhage in such sites as the subependymal and subarachnoid regions of the brain. Clifford believes that asphyxia, in the complete absence of trauma, may be responsible for hemorrhages into the cerebrospinal fluid, into the ventricles, and into the brain substance itself.

Infection as a cause of neonatal mortality still ranks as one of the leading and potentially curable factors. MacGregor, in a survey of 618 neonatal deaths, reported in 1946, found that 190 (30.7%) were attributable to an infectious process. Even more remarkable are her figures showing that in 214 babies dying after the third day of life, 158 (65.5%) were attributable to infection. In the Chicago study of neonatal mortality reported in 1951, 13.4% of all neonatal deaths were due to infection. Arey and Dent in their article[2] published in 1953 surveyed 102 consecutive neonatal deaths and found an incidence of infection as the primary cause of death of approximately 14% excluding congenital syphilis. In addition to this, he stated that bronchopneumonia of some degree was present in 40% of infants dying of all causes.

Hyaline membrane syndrome, another of the leading causes of mortality in the newborn period, is as yet a mysterious entity for which multiple theories of production or etiology have been postulated. As has been shown in many previous reports[12,13,14] and will be reiterated in this series, this condition is very largely confined to the premature infant except for the occasional product of a Caesarean delivery or the infant of a diabetic mother. Hyaline membrane syndrome usually has its onset clinically within the first 12 hours of life, a time at which respiratory distress from central nervous system damage and occasionally from infection may also be evident. The reason for survival in one newborn and death in another who clinically appeared to have hyaline membrane syndrome has resulted in the descriptive but nonrevealing entity of "Hyaline Membrane Disease without Membrane." Briggs and Hogg, in a recent article[4] describing the postmortem findings and "cause of death" in 102 consecutive newborns dying within 7 days after birth, ascribed 8% of the deaths to hyaline type of lungs without membrane while the usual type of hyaline membrane accounted for 33.6% of all deaths.

It has been stated repeatedly by various observers that clinically an infant with intraventricular hemorrhage may be clinically indistinguishable from one with hyaline membrane disease. In fact, in many instances, these two conditions are coexistent and the cause of death may be because of either one or a summation of the two. Bronchopneumonia may also be present at birth, often having been contracted *in utero* or during the birth process (via aspiration of amniotic sac contents, secondary to prolonged ruptured membranes, secondary to prolonged labor, intrauterine sepsis, or as has been mentioned before due to intrauterine asphyxia). The clinical picture of pneumonia in the first 24 hours of life may closely resemble that of either intraventricular hemorrhage or hyaline membrane dis-

ease[1] and must be considered in the differential diagnosis. Arey and Dent have shown in their study that 22 of 102 newborn infants died as a result of inflammatory lesions (21%). Eleven of these lived less than 24 hours.

Hence, since the response of the newborn is limited, no matter what the type of exciting factor, a variety of pathologic processes such as hemorrhage, trauma, infection, asphyxia may produce a similar and confusing picture in the early neonatal period. The importance of this is easily understandable when one realizes that despite our ineptness in the treatment of many of the problems of the newborn, infection hopefully is amenable to proper and adequate antibacterial treatment if started early and continued for a sufficiently long period. Diagnosis, therefore, in the immediate and early neonatal period becomes of prime importance. Bacteriologic, roentgenographic, and other indicated studies should be used as aids to differentiate the type of disease and as a guide to proper therapy. Only through full utilization of all available diagnostic aids as well as a clear concept of the problems in the neonatal period and their relative similarities and differences can one hope to improve the care of the newborn in distress.

PURPOSE. It is the purpose of this paper to present the incidence of infection as a cause of death during the neonatal period. In so doing, a statistical comparison of the major causes of death in the early neonatal periods will be given along with a graphic picture comparing the similarities and dissimilarities of three of the major causes of death in this period, namely, intraventricular hemorrhage, pulmonary hyaline membrane syndrome and infection. As far as possible, the infectious causes of death will be related to known pre-, peri-, or postnatal complications. The results of bacteriologic studies both premortem and postmortem will be presented and the relation of antibiotic therapy to these studies and to the course of the patient's disease will be presented.

Finally, the results of this investigation will be compared with those of other writers with the purpose of evaluating the use of antibiotic and chemotherapeutic agents.

Method of Study. The present study was carried out by means of a review of all deaths which occurred over a 2-year period in the newborn nurseries at Temple University Hospital (January, 1956, through December, 1957). The clinical as well as the postmortem findings, as reported in the neonatal mortality form completed on every neonatal death, were screened for evidence suggestive of infection as a cause of or major contributor to death. All suspected deaths were reviewed by surveying the mother's chart and the infant's newborn and nursery chart which contained pertinent information regarding prenatal history, type of delivery and existent problems and complications as well as condition of the infant at birth. The pediatric resident's initial examination and progress notes were reviewed and his findings were tabulated in his own words rather than interpreted with possible loss of meaning by a second observer. Laboratory studies including pre- and postmortem cultures were tabulated. Microscopic slides were reviewed on the suspected cases by James B. Arey, M.D. Our study differs from the usual neonatal mortality figures since the included patients were limited primarily to the newborn nursery period and follow-up of all births through the first 28 days of life was not possible.

Table 1 gives a statistical breakdown of births and deaths at Temple University Hospital from January, 1956, through December, 1957. In reviewing deaths from all causes, the number of newborns who received antibiotics sometime during their lifespan was 70 or 37.8% of all deaths.

The neonatal death rate for Philadelphia for the year 1956–1957 was 23.3 and 24.2 per 1000 live births.

Overall mortality rate was 3.2% or 32 per 1000 live births. (A live birth is

defined as any birth in which there is evidence of either respiration or heart beat following delivery.)

TABLE 1.—BIRTHS AND NEONATAL DEATHS, TEMPLE UNIVERSITY HOSPITAL, 1956–1957

Total births	5784
Full term	5177
Premature	607 (10.5% of all births)
Total deaths	185
Full term	41
Premature	144 (77.8% of all deaths)

Of the 185 deaths, 176 postmortem examinations were obtained and completed (postmortem rate of 95.1%). Table 2 presents the pathologic findings deemed the major causes of death in the 176 necropsied patients, based on correlation of the clinical and pathologic findings.

A comparison of these findings may be made by reviewing the findings of several other investigators who have previously reported large series of neonatal deaths. Table 3 is from the study reported by Arey and Dent, slightly modified for the sake of comparison.

During the 2-year period of our study, no newborns died of congenital syphilis.

Table 4 represents the study reported by MacGregor[15].

Analysis of the records at Temple University Hospital shows the four major contributors to neonatal mortality to be asphyxia, infection, intraventricular hemorrhage, and pulmonary hyaline membrane disease (these account for 57% of all deaths). Theoretically, at least, the first three may be related closely with asphyxia as the initiating factor. Intracranial hemorrhage

TABLE 2.—MAJOR CAUSE OF DEATH (CLINICAL AND PATHOLOGIC) IN 176 CONSECUTIVE DEATHS

Cause of Death	*Term*	*Premature*	*Total*	*% of Total*
Intracranial Hemorrhage	2	32 (31 IV)	34	19.3 (20)
Infection	7	20	27	15.4
Pulmonary Hyaline Memb.	1	21	22	12.5
*Intrauterine anoxia	10	9	19	10.8
Congenital anomaly	11	1	12	6.8
Miscellaneous (Erythroblastosis, Pulm. hemorrhage, Pulmonary edema, Glial swelling, Pulm. hyal. memb. without membrane)	6	14	20	11.3
†Undetermined (includes immaturity and undetermined)	3	39	42	23.8
Totals	40	136	176	

*Intrauterine anoxia depends upon the finding of aspiration of an excessive amount of amniotic debris (microscopic examination of the lungs).

†Infants weighing between 500 and 1000 gm. are considered as previable. Infants weighing less than 500 grams are considered nonviable. In this series, 39 undetermined causes of death are listed for prematures. These are broken down as follows:

Greater than 1000 gm.	11
500 to 1000 gm.	12
Less than 500 gm.	16

sufficient to cause death was found in 20% of those necropsied. Thirty-one of 34 were intraventricular hemorrhages found in premature infants. Of special interest is the fact that 10 of the 31 infants with intraventricular hemorrhage also had evidence of some degree of pulmonary hyaline membrane at the time of postmortem examination. The cases listed as "cause of death undetermined" include a significant number of prematures in the previable and nonviable weight range (18 of 42 weighed less than 1000 gm.). Many of these may have been assigned to the category often labeled as "immaturity" but for the sake of this paper were included under undetermined since no anatomic cause of death could be demonstrated. It is to be noted that diarrheal disease of the newborn caused no deaths over this 2-year study period.

In Arey and Dent's previously reported series there were almost identical percentages for intrauterine anoxia and infection. The increase of intracranial hemorrhages in our series may well be related to the larger number of very small premature infants included. The decreased number of patients dying as a result of infection as compared with MacGregor's series, is difficult to explain since the latter report gives no breakdown of types of infection. The similarity of our findings with Arey and Dent's as regards infection may be interpreted to show that a persistently large number of babies still die as a result of infection even in this age of increasing use of antibiotics both prophylactically and therapeutically. As stated previously, 38% of babies dying of all causes received antibiotic or chemotherapeutic

TABLE 3.—CAUSE OF DEATH IN 102 CONSECUTIVE NEONATAL DEATHS (PATHOLOGIC FINDINGS) (Arey and Dent[2])

Cause of Death	*Term*	*Premature*	*Total*	*% of Total*
Intracran. Hemorrhage	0	12 (11 IV)	12	12
Infection	1	13	14	14
Pulm. Hyal. Membrane	0	15	15	15
Intrauterine anoxia	6	5	11	10
Congen. Anomalies	6	4	10	10
Congenital syphilis	0	8	8	8
Miscellaneous	3	14	17	16
Undetermined	2	13	15	15
Totals	18	84 (82%)	102	100%

TABLE 4.—CAUSE OF DEATH IN 182 NEONATAL DEATHS REPORTED BY MACGREGOR

Cause of Death	*Term*	*Premature*	*Total*	*% of Total*
Intracran. Hemorrhage	31	140	171	27 6
Infection	64	126	190	30 7
Asphyxia	14	67	81	13 1
Congen. Anomalies	42	23	65	10 5
Miscellaneous	24	25	49	7 9
Prematurity	0	55	55	9 0
Not ascertained	7	0	7	1 0
Totals	182	436 (70%)	618	

It should be noted that no mention is made of pulmonary hyaline membranes.

agents some time prior to their death.

We have analyzed in detail the records of 27 newborns whose deaths can be attributed mainly to infection. Of these infants, 24 had received antibiotic therapy at some time during their life; 11 immediately after birth and for varying lengths of time thereafter. Indications in the majority of infants were prolonged ruptured membranes, prolonged labor, prolonged resuscitation, or respiratory distress at birth. Twenty of the 27 were premature infants (75%). One mother had received antibiotics in the 24-hour period prior to delivery because of pneumonia.

Maternal history revealed the following complicating factors:

Prediabetes	2	
Diabetes	1	(with pneumonia and acidosis)
Respiratory infection	1	
Genitourinary infection	2	
No prenatal care	3	
No apparent complications	18	
Total	27	

A total of 9 of the mothers of these infants, therefore, had apparent complications prior to delivery.

The history revealed the following complications of delivery, present in 14 cases.

Prolonged ruptured membranes	7
Unsterile delivery	5
Resuscitation (endotracheal)	4
No apparent complications	13

In reviewing the history of the pregnancy, delivery, labor, and immediate condition of the baby, the mothers of 20 of the 27 infants who died of infection (75%) had had some complication other than no prenatal care.

Of 13 blood cultures taken premortem, 6 were positive. The following organisms were isolated from the blood: *E. coli* (2), *A. aerogenes* (3), *Staphylococcus aureus*, coag. pos. (1). The preponderance of Gram-negative organisms is obvious. In 4 of 8 infants dying with bronchopneumonia, nasopharyngeal cultures were positive for possible pathogenic organisms while 4 others had no cultures. Eleven of 13 infants dying as a result of sepsis had positive nasapharyngeal or blood cultures while in 2 no cultures were taken. Five of 6 nasopharyngeal cultures revealed abnormal organisms, which correlated well with postmortem findings. Four of 8 blood cultures were positive revealing Gram-negative bacteria (coliforms) in 3 instances and a *Staph. aureus* coag.+ on one occasion.

Cause of Death	*Neg. Culture*		*Positive Culture*	*No Culture*
Peritonitis	(1)		1	
Bronchopneumonia	(8)		4	4
Sepsis	(13)		11	2
Staph. pneumonia	(1)		1	
Moniliasis	(1)			1
Herpes simplex	(1)	1		
Meningitis	(2)		2	
Totals	27	1	19	7

CASE 1 was a 9 lb. 10¼ oz. full-term infant of a prediabetic mother who previously had delivered a 10 lb. infant. Baby was delivered under unsterile conditions. Immediate condition was good. No antibiotics were given. The infant died suddenly with apnea as the presenting sign at 32 hours of age. Postmortem examination revealed severe bronchopneumonia, aspiration of meconium, and hyperplasia of the islets of Langerhans.

CASE 2 was a 3 lb., 5¾ oz. premature baby born uneventfully under sterile conditions. History revealed prolonged ruptured membranes (probable). Immediate condition was good. Chloromycetin was given for the first 2 days of life. Nasal discharge was noted at 7 days of age. A nasopharyngeal culture was done and Chloromycetin was restarted. The infant died at 9 days of age following several hours of labored respirations. Nasopharyngeal culture was reported as *E. coli*. Postmortem examination revealed severe laryngotracheitis and softening of areas of the brain. Blood culture was not reported.

CASE 3 was a 3 lb. 10 oz. premature baby (gestation 32 weeks). History revealed prolonged rupture of membranes (3 days). Delivery was unsterile after a 2-hour labor. Immediate condition was fair with some respiratory distress. Chloromycetin was given from birth. Because of lethargy, poor color, and explosive stools apparent on the 4th day and progressive thereafter, penicillin and streptomycin were added on the 7th day. Stool culture was negative for pathogens. Blood culture showed no growth. The infant died on the eighth day. Postmortem examination revealed meningitis, oomphalitis and glial swelling. Postmortem blood culture showed no growth.

It is to be noted that those signs or symptoms most commonly associated with pulmonary hyaline membrane are respiratory in nature, namely, *grunting, retraction of chest cage,* and *cyanosis.* Those symptoms or signs usually associated with intraventricular hemorrhage are usually related either to the respiratory system or the central nervous system: *gasping* respirations, *apnea, flaccidity.* Cyanosis is fairly common in both intraventricular hemorrhage and pulmonary hyaline membrane disease.

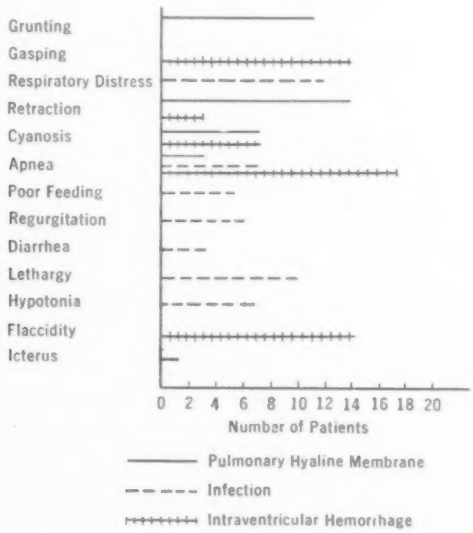

Fig. 1.—Initial symptoms as related to diagnoses.

Because of the diagnostic problem which exists in the initial newborn period, it was felt that it would be worthwhile during this study to attempt to show the major similarities and dissimilarities present in the cases of those babies whose cause of death was intraventricular hemorrhage, pulmonary hyaline membrane or infection.

Figure 1 presents a graphic representation of initial symptoms as related to diagnosis (intraventricular hemorrhage, pulmonary hyaline membrane, infection).

Infection produces signs and symptoms referable generally to the central nervous system, respiratory system, and gastrointestinal tract with *respiratory distress, poor feeding and regurgitation* of feedings, *lethargy* and *hypotonia* being the common findings.

Hypothermia was evident on the temperature charts but not included in most of the attending physician's notes.

Eight of 10 infants dying with pneumonia were noted to exhibit signs suggestive of central nervous system damage or involvement.

Figure 2 presents a graphic picture of the time of onset of symptoms as related to diagnosis (intraventricular hemorrhage, pulmonary hyaline membrane, or infection). It may be noted from this chart that symptoms associated with pulmonary hyaline membrane syndrome almost always are noted within the first 12 hours of life. Symptoms associated with intraventricular hemorrhage have their highest incidence in the first 12 to 24 hours but may occasionally occur during the second, third or fourth days. Infection

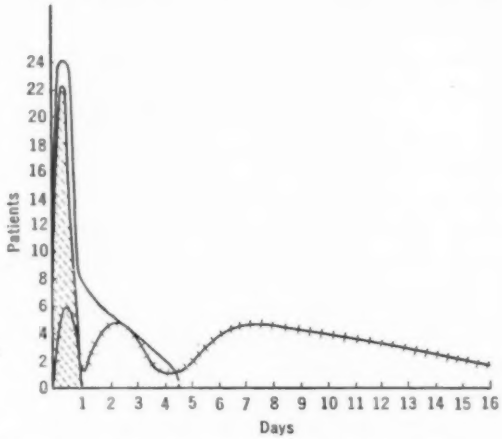

Fig. 2.—Time of onset of symptoms as related to diagnosis.

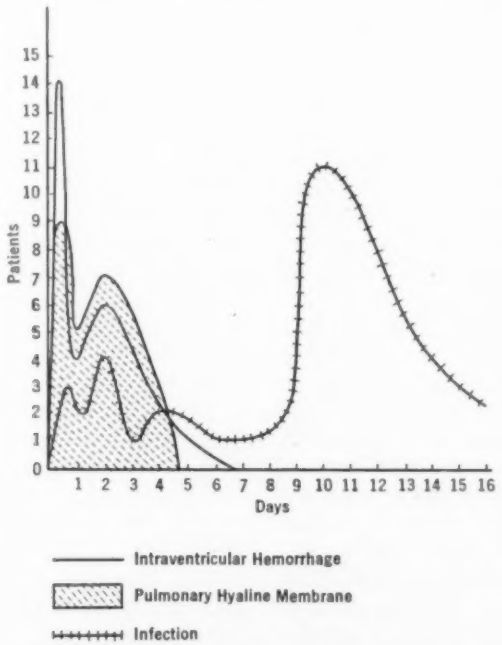

Fig. 3.—Time of death as related to diagnosis.

generally produces signs of distress after the fourth day with increasing incidence after 6 to 7 days. Signs and symptoms of infection during the first 24 hours do occur and are most often associated with infections contracted *in utero*. The appearance of symptoms suggesting infection in the first few days of life should make one highly suspicious of an infection contracted either *in utero* or during the birth process.

Figure 3 presents a graphic picture of the time of death as related to diagnosis (intraventricular hemorrhage, pulmonary hyaline membrane, or infection). It may be noted that most deaths due to pulmonary hyaline membrane occur during the first 24 to 48 hours. In our series, a few infants dying as late as the fourth day exhibited typical pathologic findings in the lungs. Death due to intraventricular hemorrhage reaches its peak incidence during the first 24 hours with a second peak during the second to fourth days. One infant died on the 6th day with a large intraventricular hemorrhage. Delayed evidence of hemorrhage and death are probably related to subependymal hemorrhage with subsequent rupture into the ventricular system. Infectious causes of death may occur early but the greatest incidence is after the first week. Most deaths occur during the second week of life.

Discussion. The great number of premature infants dying as a result of pulmonary hyaline membrane and intraventricular hemorrhage will not be discussed here except to express the feeling that since the pediatrician has so little to offer therapeutically in these cases, we must look to the physicians providing prenatal care and hope that they can in some way reduce the large number of premature deliveries since it is well recognized that the most effective treatment presently available for both pulmonary hyaline membrane disease and intraventricular hemorrhage is prevention, that is, prevention of prematurity[8].

Neonatal mortality of significant degree is present today as it was 10, 20, and 30 years ago. Despite newer and supposedly better nursery physical plants and despite frequent use of antibiotics and oxygen and other therapeutic agents a rather large number of newborns die as a result of infection.

These infections can probably be divided into three main categories, namely, those acquired prior to birth, those acquired during the birth process, and those acquired after birth[17]. Infections acquired *in utero* may represent blood-born infections with transplacental invasion such as toxoplasmosis or bacteremia from an infectious focus in the mother such as pneumonia or pyelonephritis. Prompt and adequate therapy of infection in the pregnant woman is certainly of utmost importance. Retrograde infection via the vagina especially in the presence of prolonged ruptured membranes is well recognized. It is the practice of some obstetricians to treat such patients with antibiotics or to induce labor, or both, when possible. Our series has shown that a fairly large number of newborns whose death was due to infection had been delivered following prolonged ruptured membranes in the mother (7 of 27; 25%). In 4 of these 7, cultures revealed the presence of Gram-negative organisms either in the blood or nasopharynx.

Unsterile delivery, often the result of a premature and precipitous labor, certainly increases the risk of infection during the birth process as does prolonged labor and the presence of maternal infection along the birth canal. Our study revealed 5 unsterile deliveries among the 27 infants who died with infection. Possibly 3 of these

deaths could be related to the complicated delivery. Infections acquired *in utero* and during the birth process would be expected to produce signs or death early in the neonate's life. Pneumonia, sepsis, meningitis, and other conditions, occurring in the first 24 to 48 hours probably represent this type of etiology. Infections acquired during this period in some instances can cause death later especially if suppressed by antibiotics for several days. We have seen this in a number of instances when within 24 to 48 hours after stopping antibiotics signs of distress suddenly blossom forth. Even when recognized and prompt steps are taken to re-institute treatment an alarmingly large percentage of these infants appear to go rapidly down hill and die.

Infections acquired after delivery are mainly those of environmental hazards. Both nursery and rooming-in plans are advocated by various groups. Neither seems to offer the ideal way of handling newborns in order to avoid infection. Both mothers and visitors are often carriers of pathogenic organisms which pass readily to the baby via common contactants or droplet infection[20]. The problem of the carrier[21] in the nursery especially as regards staphylococcal infections has been commented on by many authors recently following the appearance of antibiotic-resistant staphylococcal organisms as the cause of epidemics in some nurseries. Although staphylococcal infections have not been uncommon in our nursery only 4 of the lethal infections were proven to be produced by the staphylococcus. The Gram-negative coliform group of bacteria still ranks in first place as the cause of newborn infections[11,22]. Since, in many instances, these bacteria too are highly resistant to the commonly used antibiotics, they must be thought of in much the same light as the staphylococcus.

Various suggestions regarding skin care to newborns such as hexachlorophene baths, dry skin technique, dye application to the umbilical cord, and others have been promoted. Most likely no one of these is any better than the care and technique with which it is carried out. If ordinary aseptic technique were carried out by conscientious and unharried nursery personnel, it is very likely that many cross-infections would never occur.

Prevention of infection through careful prenatal care, patient education, optimum delivery room technique, and conscientious alert nursery care offers the best solution to our problem. The pediatrician must be aware of the problem concerning each infant as regards complications in the prenatal and perinatal periods. He must be cognizant of the fact that newborns and prematures especially react in certain limited ways to many various stimuli. As we have shown, infection, intracranial hemorrhage, or pulmonary hyaline membrane disease may all occur during the same periods. Clinically, they may at times closely resemble one another. Since infection may be fatal in an extremely short period of time in this age group, diagnosis and treatment must be carried out without delay. In certain instances, antibiotics are probably indicated even in the absence of signs of infection. Among these are prolonged ruptured membranes, prolonged labor, unsterile delivery, unusual respiratory distress, prolonged resuscitation measures, infection in the mother at the time of delivery or during the next 24 to 48 hours, and possibly infants of diabetic mothers.

It is strongly urged that cultures from indicated sites be taken prior to antibiotic therapy (for example, axilla at birth, nasopharynx at birth or shortly

thereafter, blood, spinal fluid, urine, and others). Treatment without this information is blind and often fruitless.

Bacteriologic studies in this series confirms the preponderance of infections caused by the Gram-negative enteric bacteria. It should be noted that infections occurring in the first few days and probably contracted *in utero* or during birth most often represent Gram-negative bacillary infections and should be treated accordingly. Chloromycetin was used in many of the infants and probably is as good a choice of drug as any for initiating treatment. However, in several instances, studies showed resistant organisms sensitive to antibiotics not commonly used. Therapy must be guided accordingly. Infections after the first week are more likely to show various organisms, for example, the resistant *Staphylococcus aureus*. Therapy of such infections should provide for this as well as the Gram-negative bacteria.

Prevention of infection remains a nebulous subject. This study cannot be used as an aid or guide to the value of antibiotics in prevention of infection since we have no control series nor any real idea of the incidence of infections that did not result in death. It would be our observation that certainly at this time the use of antibiotics provides no real protection in many cases since a rather large number of the newborns in our series who received antibiotics from birth either developed infection or had contracted infection, prior to or during birth, which did not respond to treatment. As noted previously, our statistics compare readily with Arey and Dent's study which was done before the availability of most modern antibiotics.

Summary. The results of a review of neonatal mortality confined for the most part to newborn nursery patients at Temple University Hospital during 1956–1957 has been presented. The causes of death have been tabulated statistically and a detailed summary of each patient who apparently died as a result of infection has been presented. Bacteriological cultures have been reviewed as related to etiologic agents and the importance of the Gram-negative organisms and the *Staphylococcus aureus* has been emphasized. Antibacterial treatment was reviewed in each case along with the reasons for treatment. In many instances, it was apparent that such treatment was ineffectual. The results of our study were compared with those of other investigators and in most instances were similar.

Finally, the similarities and dissimilarities of pulmonary hyaline membrane syndrome, intraventricular hemorrhage, and infection are graphically presented.

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REFERENCES

(1) **Arey, J. B., and Arey, H. M.:** Pediat. Clin. N. America, p. 52, February, 1957. (2) **Arey, J. B., and Dent, J.:** J. Pediat., **42**, 1, 1953.
(3) **Beaven, D. W., and Burry, R. F.:** Lancet, **2**, 211, 1956. (4) **Briggs, J. N., and Hogg, G.:** Pediatrics, **22**, 41, 1958. (5) **Bundesen, H. N.:** J. Am. Med. Assn., **157**, 1384, 1955.
(6) **Clifford, S. H.:** J. Pediat., **18**, 567, 1941. (7) Idem: New England J. Med., **232**, 42, 1945. (8) Idem: J. Am. Med. Assn., **153**, 473, 1953.
(9) **Forshall, I.:** Arch. Dis. Child., **32**, 25, 1957.
(10) **Gellis, S. S., Ed.:** Yearbook of Pediatrics, p. 116, 1957–1958.

(11) **Hoffman, M. A.**, and **Finberg, L.**: J. Pediat., **46**, 626, 1955. (12) **Landing, B. H.**: Pediatrics, **19**, 217, 1957. (13) **Lynch, M. J. G.**: J. Pediat., **48**, 165, 1956. (14) **Lynch, M. J. G., Mellor, L. D.**, and **Badgery, A. R.**: Ibid., **48**, 602, 1956. (15) **MacGregor, A. R.**: Brit. Med. Bull., **4**, 174, 1946–1947. (16) **Miller, H. C.**, and **Behrle, F. C.**: Pediatrics, **14**, 93, 1954. (17) **Moncrieff, A.**: Brit. Med. J., **1**, 1, 1953. (18) **Pennoyer, M. M.**, and **Sullivan, M. P.**: J. Pediat., **44**, 258, 1954. (19) **Schaffer, A. J., Markowitz, M.**, and **Perlman, A.**: J. Am. Med. Assn., **159**, 663, 1955. (20) **Smith, R. T.**: A.M.A. J. Dis. Child., **92**, 45, 1956. (21) Idem: Ibid., **95**, 461, 1958. (22) **Watson, D. G.**: J. Pediat., **50**, 352, 1957.

SUMMARIO IN INTERLINGUA

(See page 740 for original article)

Le Effecto del Addition de Hydralazina o Chlorothiazido a Agentes de Blocage Ganglionic in le Tractamento de Hypertension Sever

1. Chlorothiazido (1 g per die) o hydralazina (400 mg per die) pare esser utile in que illos permitte reducer le dosage de drogas de blocage ganglionic in le tractamento de hypertension.

2. Iste effecto es generalmente apparente pauc septimanas post le institution de chlorothiazido e durante le secunde trimestre de tractamento con hydralazina.

3. Nulle intolerabile effecto lateral se manifestava post le addition de chlorothiazido. Dece-duo de 16 patientes exhibiva reducite requirimentos de drogas de blocage e minus numerose effectos lateral.

4. Quatro ex 17 patientes recipiente hydralazina in supplementation de agentes de blocage ganglionic non poteva tolerar le droga a causa del effectos lateral. Septe monstrava nulle reduction de lor requirimentos de drogas de blocage ganglionic e nulle reduction orthostatic del gradiente de tension sanguinee. Le remanente 6 obteneva un considerabile beneficio.

5. Es concludite que hypertension de forma sever debe esser tractate initialmente con chlorothiazido e blocage ganglionic. Le addition de hydralazina in un curso de al minus 3 menses va provar se capace a reducer additionalmente le requirimento de certe patientes pro drogas de blocage ganglionic.

GYNECOLOGY AND OBSTETRICS

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RECENT ADVANCES IN THE DETERMINATION OF THE ESTROGENS

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DURING the last 6 years important advances have been made in the study of estrogens and their metabolism. An estrogen (Gk., oistros, mad desire, and gennao, produce) is defined as any compound regardless of source or chemical composition which will induce cornification of the vaginal epithelium in the castrate rat or mouse[81]. Although these substances are regarded as sex hormones, they play a prominent role in the physiology of growth and of certain metabolic processes that take place in the body.

Until 1953, only three different but closely related phenolic steroids had been isolated from the urine of pregnant women. These estrogens: estrone, estradiol-17β and estriol, were also known to be present in the urine of normal menstruating women, in postmenopausal women and in the urine of men. Since 1953, eight more naturally occurring estrogenic steroids have been isolated (see Table 1). The estrogenic steroids are characterized by (1) an aromatic Ring A, (2) oxygen substituent at C-17 and (3) a phenolic OH group at C-3 which gives the compounds weakly acidic properties.

This review will deal with (1) the estrogens recently isolated from human sources, (2) the determination of estrogens in urine and blood and (3) certain aspects of their metabolic relationships. Recent reviews cover portions of these subjects, to which reference will be given rather than reiteration. It is not within the scope of this paper to review the fine work accomplished with the metabolism of estrogens *in vitro* and in lower animals[7-8,14,22,36,37,48,59,67,69-75,79,89,91,92,110,112,129,131-134,140,147,159-161,164,166-169,173,175,176].

THE NEWLY ISOLATED ESTROGENS. The chemical and biological data concern-

TABLE 1.—ESTROGENS IN HUMANS 1929–1959[151]

Compound	First isolated and identified in humans Reference	Experiment
1. Estrone	1929 (*a*) Doisy *et al.*[81] (*b*) Butenandt[33]	Natural product in preg. urine
2. Estriol	1930 (*a*) Marrian[103] (*b*) Doisy *et al.*[82]	Natural product in preg. urine
3. Estradiol-17β	1939 Smith, Smith, Huffman *et al.*[76,147]	Natural product in preg. urine
4. 16-ketoestrone	1953 Serchi, G.[142]	Natural product in preg. urine
5. 16-epiestriol	1955 Marrian and Bauld[101]	Natural product in preg. urine
6. 16-ketoestradiol-17β	1956 Levitz *et al.*[90]	In urine as product of estradiol 17β-16-C^{14}*
7. 16α-hydroxyestrone	1957 Marrian *et al.*[102]	Natural product in preg. urine
8. 2-methoxyestrone	1957 (*a*) Kraychy and Gallagher[85,86] (*b*) Engel *et al.*[58]	In urine as product of estradiol 17β-16-C^{14} In urine as product of estradiol 17β-16-C^{14}
9. 18-hydroxyestrone	1958 Loke, Marrian *et al.*[94]	Natural product in preg. urine
10. 16β-hydroxyestrone	1958 Layne and Marrian[88] 1958 Brown, Fishman and Gallagher[23]	Natural product in preg. urine In urine as product of estradiol 17β-16-C^{14}
11. 17-epiestriol	1958 Breuer, Nocke and Knuppen[21]	As product of 16 OH-estrone incubated with human liver.

*Later isolated and identified as natural product in human pregnancy urine (Layne and Marrian, 1958).[88]

ing estrone, estradiol-17β and estriol, have been thoroughly documented in both textbooks and several excellent papers[9,17,34,41-43,53,55,57,60,61,64,68,71,81,87,97,104,114,115,119,120,122,126,141,148,152,154,172,178]. The following is a brief discussion of some of the known properties of the newly identified estrogens.

16-Ketoestrone. Serchi and Poggi[142] reported finding this compound in human urine. Slaunwhite and Sandberg[144] were able to isolate and identify it after the administration of 1 μc. (370 μg.) of estradiol-17β-16 C^{14} intravenously to a 32-year-old woman during the luteal phase of her menstrual cycle. No 16-ketoestrone was found in the urine of 2 young women so treated who were not in the luteal phase of the menstrual cycle.

16-Epiestriol. In 1955, Marrian and Bauld[101,171] isolated from the urine of pregnant women a new Kober chromogen, which was identified as 16-epiestriol. Estimation by a method, not strictly quantitative, revealed that the concentration in pregnancy and in menstrual cycle urines are about the same as those of estradiol-17β. 16-Epiestriol induces vaginal cornification in castrate mice and rats but is considerably less potent than estriol in this respect. In these experiments the ratio of activities (estriol/16-epiestriol) was approximately 20:1. 16-Epiestriol was the weakest of the six estrogens tested (estrone, estradiol-17β, estriol, 16α and 16β-hydroxyestrone), in promoting uterine growth in ovariectomized rats. It has been found that it showed in common with estriol the property of suppressing uterine growth induced by estradiol-17β[163]. Huggins and Jensen[77] showed that estriol and 16-epiestriol inhibit to a limited extent the uterine growth induced by estrone administered concurrently.

16-Ketoestradiol-17β. Levitz, Spitzer, and Twombly[90] reported the identification in human urine of 16-ketoestradiol-17β after the administration of estradiol-17β-16-C^{14}. One and five tenths per cent of the radioactivity was accounted for by this compound. Confirmation of the presence of this substance in human urine has been reported by Layne and Marrian[88].

16α-Hydroxyestrone. This compound has been isolated from the urine of pregnant women by Marrian, Loke, Watson and Panattoni[102]. It is thought by Marrian to be a precursor of estriol[103]. Determinations of 16α-hydroxyestrone have given values as high as 3 mg. per 24 hours for urine of late pregnancy and 25 μg. per 24 hours for menstrual cycle urine. It is evident that 16α-hydroxyesterone is of considerable quantitative importance. Loraine[96] has shown the estriol and 16α-hydroxyestrone are approximately equipotent when assayed by the vaginal smear test in castrate mice. The data of Velardo[163] shows that 16α-hydroxyestrone has greater potential in inducing uterine growth than either 16β-hydroxyestrone or estriol but less than that of either estradiol-17β or estrone in ovariectomized rats.

2-Methoxyestrone. This compound was first isolated by Kraychy and Gallagher[85,86] and confirmed by the work of Engel, Baggett and Carter[58]. One gram of estradiol-17β-16-C^{14} was administered to a human and 8% of the radioactivity in the urine was accounted for by 2-methoxyestrone. Biologically the substance is a very weak estrogen with activity less than 1/20,000 that of estradiol-17β as judged by the intravaginal assay of Emmens. It failed to exhibit fluorescence with sulfuric acid but gives a positive Kober and Zimmermann reaction. As Kraychy and Gallagher state, two facts about the biochemical transformation of phenolic steroids become very significant from this isolation of 2-methoxy-

estrone in the human. The oxidation of the aromatic ring is achieved under conditions *in vivo* and this in all probability is a preliminary stage to fission of the carbon skeleton. It may be interpreted that the metabolism of estrone or estradiol-17β is accomplished in two separate stages, namely, oxidation and subsequent methylation. The introduction of a methoxyl group is a novel reaction in the steroid field. This reaction is widespread in the plant kingdom and it now appears that orthomethylation takes place in the human body processes.

18-Hydroxyestrone. Isolation and identification of this compound from the urine of pregnant women has been reported recently by Loke, Marrian, Johnson, Meyer and Cameron[94]. No data as to its physiologic potential has yet been reported.

16β-Hydroxyestrone. This compound has been identified in the urine of women with cancer of the breast after 0.5 mg. of estradiol-17β-16-C^{14} was administered intravenously[23,88]. It is believed to be a precursor of 16-epiestriol. One-third of the ketol fraction and approximately 3% of the urinary radioactivity consisted of 16β-hydroxyestrone. Velardo[163] showed that 16β-hydroxyestrone has greater potential for inducing uterine growth than estriol, but less than that of estradiol-17β, estrone, and 16α-hydroxyestrone.

17-Epiestriol. This compound has recently been tentatively identified by Breuer, Knupper, and Pangels[21] when 16-ketoestrone was incubated with slices of normal human liver and ovaries. The amount produced was quite small compared to the other metabolites found. No identification in urine has been reported.

DETERMINATION IN URINE. A great handicap in the study of estrogens is the fact that these compounds occur in microgram amounts in the urine, blood and tissues. Only in pregnancy does the urinary concentration rise to milligram quantities that facilitate isolation and positive identification. Early methods for estimation of estrogenic activity have been based on bioassay. However, Loraine[98] has stated that estrogen assays in human urine should now be conducted by chemical rather than by biological methods. Reliable chemical assay figures are now available for the excretion of estrone, estradiol-17β and estriol in all human urine[24,26,29,31].

Estrogens present in the urine occur mainly as conjugates with glucuronic acid and a smaller portion with sulfuric acid. Prior to extraction and determination these conjugates usually are hydrolyzed. Recent reports by Smith and Smith[150], Smith and Blackman[149], Straw, Katzman and Doisy[156] and a review by Bauld and Greenway[11], will give the reader an excellent detailed evaluation of the various hydrolytic procedures.

The work of Brown[25] and of Bauld[10] in developing methods for the chemical determination of estrone, estradiol-17β and estriol in urine has been a significant contribution to this field. Their methods are felt to be the best available for estimation of estrone, estradiol-17β and estriol[55,98]. Amounts of 5 μg. and above can be determined with precision. The accuracy from 1 to 5 μg. is fair, but below 1 μg. it is poor. The methods of Brown differ from Bauld's as to separation and purification of the estrogen containing fractions but in both a modified version of the Kober color reaction is used for final estimation. At present neither method can measure any of the newly isolated estrogens. It must be emphasized that these methods are complex procedures necessitating well trained personnel, and have not reached the stage of routine clinical laboratory usage. Four

to 6 complete estimations can be accomplished in 2 working days by one qualified person.

Eberlein *et al.*[54] have developed a "simplified chemical method for the routine determination of urinary estriol." They reasoned that measurement of urinary estriol alone should prove adequate for clinical purposes since the ratio of one estrogen to another varies little. Exceptions are pregnancy and the newborn, when the amounts of estriol are disproportionate to those of estrone or estradiol-17β[22,46,105]. By their method, estriol excretion was found to rise with increasing age in normal children and to vary little between males and females of the same age until adolescence is reached. Estriol excretion as high as 124 μg. per 24 hours was found in cases of untreated adrenal hyperplasia. This method enables a technician to accomplish the estrogen determination of six samples in a working-day. It offers great promise in the direction of routine chemical assay for clinical purposes.

Recently other authors have reported methods for chemical determination of estrogens in urine[4,38,57,63,66,78,83,105,118,153,155,174]. These methods in general measure phenol steroids as a group or as an estrone and estradiol-17β fraction and an estriol fraction.

Urinary Estrogens in Normal Women. Brown[30,31] studied, with his method, the urinary estrogen excretion during 16 normal menstrual cycles. He found that within the first 2 or 3 days of menstruation in a 28-day cycle the estrogen excretion is low: in the range of 4 to 22 μg. "total" estrogen per day (mean 12 μg.) "Total" estrogen is the sum of estrone, estradiol-17β and estriol. The estrogen levels rise to a well-defined peak on about the 13th day of the cycle. This peak is called the "ovulatory" or "follicular" maximum. Values range from 35 to 100 μg. (mean 57 μg.) per 24 hours, and it is shown by all three estrogens measured. The rise to the peak is usually gradual and the subsequent fall abrupt. The time interval between the peak and the onset of menstruation is usually 14 days. During this time a short period of decrease is followed by another rise, the "luteal" maximum which averages about 33 μg. daily (range 17–87 μg.). Though variations occur in most cycles, the follicular maximum exceeds that of the luteal maximum. A few days prior to menstruation the estrogen falls rapidly and by the first day of the next cycle it has again reached an average of 12 μg. daily.

The rise and fall in urinary estrone and estradiol-17β levels parallel one another, but the changes in estriol excretion tend to lag about 24 hours behind the other two. Brown[30] found no correlation between the level of the gonadotrophin peak and the estrogen peak. Nor was a correlation obtained between actual amounts of estrogen and pregnanediol excretion.

Urinary Estrogens in Endocrinopathies. In a group of 10 cases studied by Brown[31] in which there was no evidence either clinically or histologically of estrogenic stimulation, total estrogen excretion was 3.2 μg. to 9.0 μg. (mean 5.5 μg.). These values represent estrogen levels which are considered insufficient to stimulate growth of the endometrium. These estrogens are not of ovarian origin since bilateral oophorectomy had no effect on the amounts produced. They are probably derived from the adrenal cortex. McBride[99] has also reported similar values. Excretion of 9.0 μg. total estrogen per 24 hours was in the upper limits of the range found in which no endometrial stimulation occurred.

In instances of anovulatory menstrual cycles, the characteristic feature of the

urinary excretion pattern was the constancy of the amounts excreted at all times of the cycle. The estrogen levels found during anovulatory cycles were maintained in the range of 13 to 30 μg. total estrogens per 24 hours urine.

In cases of cystic glandular hyperplasia of the endometrium, total urinary estrogen levels were maintained for some time in the region of 30 μg. or more per day. The levels may remain constant as in anovulatory cycles, or rise and fall as in ovulatory menstrual cycles, but the rise and fall occurs as a broad maximum which does not resemble the sharp ovulation peak of a menstrual cycle. Peak levels may be higher than those found during normal menstrual cycle.

In cases of primary and secondary amenorrhea the estrogen levels were within postmenopausal limits. Emphasis is made that dogmatic opinion cannot be given unless estrogen assays are performed daily over a prolonged period of perhaps at least 3 weeks' duration.

Urinary Estrogens in Pregnancy. During pregnancy estrogen excretion is abundant. For some time chemical rather than bioassay has been used for their determination. There is a rise in urinary excretion of estrone, estradiol-17β and estriol throughout pregnancy; the rate of increase is most marked between the 6th and 20th week. After labor a rapid fall occurs in the output of all three estrogens. Estrone and estradiol-17β reached normal nonpregnant levels within 5 days, but it takes estriol longer, in some cases as long as 20 days. Neither Bradshaw and Jessop[19] nor Brown[26] were able to demonstrate any correlation between estrone excretion and the onset of labor. At full term the average amounts of the different estrogens excreted per 24 hours are approximately as follows[26]:

Estradiol-17β	750 μg.
Estrone	2000 μg.
16-Epiestriol	750 μg.
16α-hydroxyestrone	2000 μg.
Estriol	30000 μg.

Brown[28] has made estimates of the estrogens secreted by the placenta throughout pregnancy. He reasoned that the placenta secretes estriol as such. Since this substance is found in much greater concentration than either estrone or estradiol-17β, it cannot be a metabolite of estrone or estradiol-17β but must be secreted as such. The weight curve of the placenta parallels the estriol production curve. Different investigators have analyzed placental tissue and agree consistently that estriol is present in greater quantity than estrone and estradiol-17β[14,45,109].

Zondek and Goldberg[177] used the urinary estriol excretion as an index of placental function. By chemical assay they concluded that, from about the 20th week of pregnancy on, an estriol titer below 1,000 μg. per 24 hours indicates irreversible placental dysfunction and secondary death of the fetus. A rising titer indicates adequate placental function. They further stated that in the cases of toxemia of pregnancy with high excretion of gonadotrophin, the urinary estriol is of special prognostic importance. Under these circumstances, in spite of the death of the fetus, the urinary gonadotrophin titer may still be high, while the estriol titer is already low.

Berge[13] has shown the usefulness of serial determinations of urinary estriol in pregnancy. From a clinical point of view, it is emphasized that a great deal of investigation will be necessary for this phenomenon to be a dependable prognostic index.

Bruns *et al.*[32] and Taylor *et al.*[157] studied urinary estrogen excretion in normal and premature labor, using the chemical method of Anker[4]. A persis-

tently low level of urinary estrogens was suggestive of uteroplacental dysfunction. Sixteen patients who were delivered prematurely showed low urinary estrogen excretion and excessive uterine contractility when compared to 16 normal patients. In severe pre-eclampsia, urinary estrogens were low. These studies point to placental insufficiency as reflected by urinary estrogen measurement.

DETERMINATION IN BLOOD. The determination of the estrogens in blood or plasma by chemical methods has been much more difficult than that of the urinary content due to the exceedingly low concentration of these compounds.

In order to measure plasma estrogens, a method sensitive enough to detect these steroids in the range of 0.05 to 0.10 μg. is needed. A satisfactory chemical approach demands a suitable extraction procedure coupled with an extremely sensitive method of quantitating the isolated compounds. Fluorometric methods, in contrast to colormetric procedures, permit the detection of as little as 0.005 μg. of these compounds and offer a possible means of estimating the blood estrogens. In general the recently described methods employ solvent extraction, purification and separation of estrogens by column or paper chromatography and final estimation by fluorometry.

Various modifications of these procedures have been reported by Veldhuis[165], Nakao and Aizawa[111], Varangot[162], Diczfalusy and Magnusson[49], Aitken and Preedy[1], Breuer and Nocke[20], Slaunwhite and Sandberg[146], Ittrich[80], and Puck[121]; all for the estimation of estrone, estradiol-17β and estriol in blood. In some the free compounds were estimated and in others hydrolytic procedures were performed prior to extraction, purification and estimation. In these reports (with the exception of Slaunwhite and Sandberg) definite criteria are not presented for the identification of the final fractions that were assayed as estrone, estradiol-17β or estriol. Preliminary reports have appeared by Oertel, West and Eik-Nes[113] and Touchstone and Greene[158] to give further confirmation of the presence of these compounds in blood. Oertel *et al.* used acid hydrolysis, paper chromatography and countercurrent distribution to isolate estrone, estradiol-17β and estriol in pregnancy plasma. Positive identification was made by infrared analysis. Touchstone and Greene have presented evidence to indicate the presence of free estriol in plasma. This was done by ether extraction of plasma with column and paper chromatography for isolation, purification and identification. Final estimation was by fluorometry. A greater quantity of free estriol was found in umbilical cord plasma than in maternal plasma at delivery.

Since the determination of the estrogens in the blood is in its infancy, values have yet to be established. Preedy and Aitken[117] have reported the following estimations of three estrogens in plasma of 6 women during the luteal phase of the menstrual cycle:

Estrone	<0.060 to 0.215 μg. per 100 ml.
Estradiol-17β	<0.070 μg. per 100 ml.
Estriol	<0.015 to 0.296 ug. per 100 ml.

In 5 males the following values were obtained:

Estrone	<0.060 to 0.111 μg. per 100 ml.
Estradiol-17β	<0.070 μg. per 100 ml.
Estriol	<0.150 μg. per 100 ml.

Oertel, West and Eik-Nes[113] have reported higher values than those of Preedy and Aitken for menstruating women. No estrogens could be determined in male plasma by their procedure.

As to the gestational state, Aitken and Preedy[2,3] reported values for the

total estrogens in late pregnancy plasma as follows:

Estrone: 2.65 to 10.3 μg. per 100 ml. of plasma
Estradiol-17β: 1.25 to 2.93 μg. per 100 ml. of plasma
Estriol: 4.28 to 17.5 μg. per 100 ml. of plasma

These figures represent total estrogen, since hydrolysis was carried out prior to extraction. In studies of plasma in pregnancy, Aitken *et al.*[3] found that the estrogen levels during normal labor do not differ significantly from those in late pregnancy. No significant difference was observed between the mean levels of any of the hormones when Caesarean section samples were compared with those taken during normal labor. However, in both groups a highly significant difference between the estrone, estradiol-17β and estriol in maternal plasma as opposed to fetal plasma was found. Fetal plasma estriol levels were 5 to 6 times higher than maternal plasma, while fetal estrone and estradiol-17β were significantly lower. This high level of fetal plasma estriol was also found by Roy and Brown[130], Diczfalusy and Magnusson[49], and Touchstone and Greene[158]. The finding that human labor is not associated with a major alteration in plasma concentration of estrone, estradiol-17β or estriol is of great interest. If this is substantiated by further work, certain theories concerning the onset of labor must be revised.

Slaunwhite and Sandberg[146] have reported studies of estrogens in plasma of pregnant women. They employed countercurrent distribution, paper chromatography, fluorometric and isotopic techniques, to separate and characterize estrone, estradiol-17β and estriol from extracts of one to two liters of human pregnancy plasma. It was found that the concentration of estrone and estriol remained nearly constant (3 to 9 μg. per 100 ml. of plasma) through the second and third trimester but the concentration of estradiol-17β varied from 0 to 8 μg. per 100 ml.

A great problem in the study of blood estrogens is the actual state in which they exist in plasma. Recently several good reviews and experimental studies have appeared concerning this important problem[5,6,15,16,35,39,40,44,56,62,65,67,93,114,116,123,124,125,127,128,137,139,140,145,173]. Some excellent workers have indicated by their investigations that estrogenic substances are mostly unbound, whereas others have found a good portion bound to proteins. The consensus is that practically all blood estrogens, either free or conjugated, are bound to protein[82]. With the experimental tools at hand, the physiological disposition of these steroids will certainly be elucidated.

URINARY EXCRETION OF ESTROGEN METABOLITES. Until recently studies concerning the physiological disposition of estrogen have been somewhat unsatisfactory due to the low recoveries of the administered steroids in urine and feces. Only 10 to 25% of injected estrogens were recovered from the urine by either chemical or biological assay[114]. Using the Brown[28] method it was found that upon administering estrone or estradiol-17β an average of 16% of the injected dose was recovered in the urine as estrone, estradiol-17β and estriol. The average proportion of urinary estrone plus estradiol-17β to estriol was 55 to 45. Thus estrone and estradiol-17β are metabolized in the same manner. When estriol was administered, an average of 56% of the injected dose was recovered in the urine as estriol alone. Therefore, following the injection of estriol, there was no observable change in estrone or estradiol-17β excretion. This further substantiates the belief that estriol is a metabolite of estrone and estradiol-17β. When estrone or estradiol-17β is administered the urinary estrone and

estradiol-17β rise and fall together, the peak excretion occurring on the day of the injection. The time for urinary estrone and estradiol-17β to return to control values is 2 to 4 days. When estriol is given, the peak excretion occurs on the day after the injection and the time necessary to return to control levels is 4 to 9 days.

The advent of the tagging techniques has made possible more precise study of the fate of administered estrogens. Beer and Gallagher[12] demonstrated that the excretion of radioactivity in the urine after the injection of estrone-16-C^{14} in two nonpregnant humans, were 77 and 58% of the administered dose. The excretion of radioactivity in the feces was negligible. As Loraine[97] has emphasized, this important work makes it possible to draw two main conclusions: "The first is that urine is the main route of excretion for estrogen metabolites; this fact was not appreciated before. The second conclusion is that the urine must contain unknown metabolites other than the five known estrogens and that, from the quantitative point of view, the unknown metabolites are more important than the known metabolites."

This work has been extended by Sandberg and Slaunwhite[138], who demonstrated that a little over 80% of the administered radioactivity of 16-C^{14}-estrone or 16-C^{14}-estradiol-17β were excreted in the urine during the 96 to 120 hours following the injection of these steroids. On the average, 72% of the counts were found in the conjugated fraction, the preponderant portion in the glucuronidate form. When a group of patients with bile-fistulas (T-tube drainage) were studied, more of the radioactivity appeared in the bile than in the urine. About 50% of the radioactivity of the administered dose was found mostly as conjugates released by hydrolysis at pH 1 or by hot acid. Of non-fistula patients, about 7% of radioactivity appeared in the stools, indicating the gastrointestinal reabsorption of metabolites in bile for their subsequent urinary excretion.

Migeon, Wall and Bertrand[108] have confirmed this work, using estrone-16-C^{14} in 3 normal adults. Of the administered dose, 59.4 to 71.95% was excreted in 48 hours and 79.9% to 89.5% by the sixth day. Only 42.7 to 62.58% of the administered dose was accounted for after the various techniques of hydrolysis. The urinary glucuronide fraction consisted of estrone (8.36 to 14.75% of administered dose), estradiol-17β (2.95 to 4.94% of administered dose), estriol and more polar compounds (14.06 to 15.72% of dose), 16-ketoestrone (1.82 to 5.85% of dose), 16-epiestriol (1.40 to 3.19% of dose), a mixture of the isomers of 16-ketoestradiol and 16α- or β-hydroxyestrone (1.53 to 3.94% of dose) and a compound which could be 2-methoxyestrone representing 1.37 to 3.97%. Thus, by using istopic labeled estrogen it is possible to show the metabolic products of estrone and estradiol-17β. This explains why with methods detecting only estrone, estradiol-17β, and estriol, such low recoveries of administered estrogens are obtained.

Radioactivity is excreted much more slowly following C^{14}-estrone or C^{14}-estradiol-17β administration than that following administration of other C^{14} steroids. Following administration of C^{14}-labeled cortisol[106], testosterone[136], 11β hydroxy-androstenedione[18] or corticosterone[107] over one-third of the radioactivity is excreted in the urine in the first 4 hours and over 60 to 70% in the first 12 hours. With C^{14}-estrone or C^{14}-estradiol-17β, only 12% are excreted in the first 4 hours and about 33% after 12 hours[138].

The newly discovered estrogens will assume considerable importance in nor-

mal and pathologic processes. The extensive studies of Smith and Smith[150], and Smith and Blackham[149], using pregnancy urine give evidence that there are yet more estrogens to be isolated and identified. They have demonstrated by bioassay, the presence of estrogenic activity that could not be accounted for by the chemical determination of estriol, estrone and estradiol-17β by the Brown method. Observations to date, both bioassay and chemical analysis, indicate that 16-epiestriol, 16-ketoestrone, 16-ketoestradiol-17β, 16α-hydroxyestrone or 2-methoxyoestrone could not account for the unknowns found. Thus, in terms of estrogenic activity the unknown compounds account for a large part of the total urinary estrogens and they completely alter the picture of changes in estrogen output related to the period of gestation from that obtained when only estriol, estrone and estradiol-17β are measured. The rate of excretion of the latter increased steadily up to the onset of labor. However, when the unknowns are measured using certain hydrolytic procedures, there is a peak of excretion at 36 to 38 weeks, with a postpartum decrease in estrogen output, but when the hydrolytic procedure is changed there is a decrease at 35 to 38 weeks and a rapid prepartum increase. Until these unknown estrogens are isolated and identified, their relationship to estrogen metabolism remains obscure.

Summary. The newer analytical tools, tracer techniques, paper chromatography, countercurrent distribution, better instruments and methods for colorimetry and fluorimetry have made possible the isolation and identification in the human of 8 new estrogens since 1953. Evidence is present to indicate that there are still more unknown estrogens to be isolated and characterized.

Estrogen assays in human urine can now be performed with reasonable accuracy by chemical methods for the estimation of estrone, estradiol-17β and estriol. No procedures are yet available for accurate determination of the newly isolated estrogens. Work done to date has provided valuable information concerning estrogen metabolism in the normal menstruating woman, pregnancy and certain endocrinopathies.

Methods for estimation of the blood estrogens are being developed. Sufficient work has not been accomplished to establish with certainty the actual quantities of the estrogen present, nor the state in which they are transported. Only in the last year has the identification of estrone, estradiol-17β and estriol in plasma been reported.

The tracer techniques have been of great value in studying the metabolic fate of injected estrogens. Previously unknown metabolites can now be detected by this procedure, which has not been fully exploited. Much remains to be investigated. The unknown phenolic steroids, the mode of action, biosynthetic pathways and their relationship to the endocrinopathies provide fascinating fields for experimentation.

REFERENCES

(1) **Aitken, E. H.,** and **Preedy, J. R. K.:** Biochem. J., **62**, 15, 1956. (2) Iidem: Ciba Foundation Colloquia on Endocrinology. Boston: Little, Brown and Co., **11**, 331, 1957. (3) **Aitken, E. H., Preedy, J. R. K., Eton, B.,** and **Short, R. V.,** Lancet, **2**, 1096, 1958. (4) **Anker, R. M.:** Clin. Chem., **2**, 184, 1956. (5) **Antoniades, H. N., McArthur, J. W., Pennell, R. B., Ingerrall, F. M., Ulfelder, F.,** and **Oncley, J. L.:** Am. J. Physiol., **189**, 455, 1957. (6) **Antoniades, H. N., Pennell, R. B., Slaunwhite, W. R.,** and **Sandberg, A. A.:** J. Biol. Chem., **229**, 1071, 1958.

(7) **Baggett, B., Engel, L. L., Savard, K.,** and **Dorfman, R. I.:** Ibid., **221,** 931, 1956. (8) **Baggett, B., Engel, L. L., Baldera, L.,** and **Lammar, G.:** Endocrinology, **64,** 600, 1959. (9) **Barnes, A. C., Buckingham, J. C.,** and **Dillhoefer:** Am. J. Obst. & Gynec., **76,** 955, 1958. (10) **Bauld, W. S.:** Biochem. J., **63,** 488, 1956. (11) **Bauld, W. S.,** and **Greenway, R. M.:** *In* Methods of Biochemical Analysis. New York: Interscience Publishers, **5,** 337, 1957. (12) **Beer, C. T.,** and **Gallagher, T. F.:** J. Biol. Chem., **214,** 335, 1955. (13) **Berge, B. S. T., Weeke, A.,** and **Groen, A.:** Acta endocrinol., **24,** 31, 1957. (14) **Bever, A. T.:** Ann. New York Acad. Sci., **75,** 472, 1959. (15) **Bischoff, F., Stauffer, R. D.,** and **Gray, C. L.:** Am. J. Physiol., **177,** 65, 1954. (16) **Bischoff, F.,** and **Stauffer, R. D.:** Ibid., **191,** 313, 1957. (17) **Bongiovanni, A. M., Di George, A. M.,** and **Grumbach, M. M.:** J. Clin. Endocrinol. & Metab., **19,** 1004, 1959. (18) **Bradlaw, H. L., Hellman, L.,** and **Gallagher, T. F.:** Fed. Proc., **15,** 223, 1956. (19) **Bradshaw, T. E. T.,** and **Jessop, W. J. E.:** J. Endocrinol., **9,** 427, 1953. (20) **Breuer, H.,** and **Nocke, L.:** Acta endocrinol., **29,** 489, 1958. (21) **Breuer, H., Knupper, R.,** and **Pangels, G.:** Ibid., **30,** 247, 1959. (22) **Breuer, H., and Nocke, L.:** Ibid., **31,** 69, 1959. (23) **Brown, B. T., Fishman, J.,** and **Gallagher, T. F.:** Nature, **182,** 50, 1958. (24) **Brown, J. B.:** Lancet, **1,** 320, 1955. (25) Idem: Biochem. J., **60,** 185, 1955. (26) Idem: Lancet, **1,** 704, 1956. (27) **Brown, J. B., Bulbrook, R. D.,** and **Greenwood, F. C.:** J. Endocrinol., **16,** 41, 1957. (28) **Brown, J. B.:** Ibid., **16,** 202, 1957. (29) Idem: Acta endocrinol., **24,** 29, 1957. (30) **Brown, J. B., Klopper, A.,** and **Loraine, J. A.:** J. Endocrinol., **17,** 401, 1958. (31) **Brown, J. B., Keller, R.,** and **Matthew, G. D.:** J. Obst. & Gynaec. Brit. Emp., **66,** 177, 1959. (32) **Bruns, P. D., Taylor, E. S., Anker, E. S.,** and **Drose, V. E.:** Am. J. Obst. & Gynec., **73,** 579, 1957. (33) **Butenandt, A.:** Naturwissenschaften, **17,** 879, 1939.

(34) **Cameron, C. B.:** J. Endocrinol., **15,** 199, 1957. (35) **Cantarow, A., Rakoff, A. E., Paschkis, K. E., Hansen, L. P.,** and **Walklin, A. A.:** Proc. Soc. Exper. Biol. & Med., **52,** 256, 1943. (36) **Chang, E.,** and **Dao, T. L.:** Abstracts of 41st Meeting of the Endocrine Society, 1959.

(37) **Dancis, J., Money, W. L., Condon, G. P.,** and **Levitz, M.:** J. Clin. Invest., **37,** 1373, 1958. (38) **Dao, T. L.:** Endocrinology, **61,** 242, 1957. (39) **Daughaday, W. H.:** J. Clin. Invest., **37,** 511, 1959. (40) **Daughaday, W. H., Kozak, I.,** and **Biederman, O.:** Ibid., **38,** 998, 1959. (41) **Davis, M. E., Plotz, E. J., Le Roy, G. V.,** and **Gould, R. G.:** Am. J. Obst. & Gynec., **72,** 740, 1956. (42) **Davis, M. E.,** and **Plotz, E. J.:** Ibid., **76,** 939, 1958. (43) **Dawling, J. T., Freinkel, N.,** and **Ingban, S. H.:** J. Clin. Endocrinol. & Metab., **16,** 1491, 1956. (44) **Diczfalusy, E.:** Acta endocrinol., Supplement No. 12, 1953. (45) **Diczfalusy, E.,** and **Lindkuist, P.:** Ibid., **22,** 203, 1956. (46) **Diczfalusy, E., Tillinger, K. G.,** and **Westman, A.:** Ibid., **26,** 303, 1957. (47) **Diczfalusy, E.,** and **Axelson:** Ciba Foundation Colloquia Endocrinology. Boston: Little Brown & Co., **11,** 336, 1957. (48) **Diczfalusy, E.,** and **Halla, M.:** Acta endocrinol., **27,** 303, 1958. (49) **Diczfalusy, E.,** and **Magnusson, A. M.:** Ibid., **28,** 169, 1958. (50) **Diczfalusy, E., Menini, F., Tillinger, K. G.,** and **Westman, A.:** Ibid., **30,** 539, 1959. (51) **Doisy, E. A., Veler, H.,** and **Thayer, S. A.:** Am. J. Physiol., **90,** 329, 1929. (52) **Doisy, E. A., Thayer, S. A., Levin, L.,** and **Curtis, J. M.:** Proc. Soc. Exper. Biol. & Med., **28,** 88, 1930. (53) **Dorfman, R. I.:** Annual Review of Biochemistry. Palo Alto, California: Annual Reviews Inc., **26,** 523, 1957.

(54) **Eberlein, W. R., Bongiovanni, A. M.,** and **Francis, C. M.:** J. Clin. Endocrinol. & Metab., **18,** 1274, 1958. (55) **Eckstein, P.,** and **Zuckerman, S.:** Memoirs of the Society for Endocrinology. Cambridge, England: Cambridge University Press, 1955. (56) **Eik-Nes, K., Schellman, J. A., Lumoy, R.,** and **Samuels, L. T.:** J. Biol. Chem., **206,** 411, 1954. (57) **Engel, L. L.:** Rec. Progress in Hormone Res., **5,** 335, 1950. (58) **Engel, L. L., Baggett, B.,** and **Carter, P.:** Endocrinology, **61,** 113, 1957. (59) **Engel, L. L., Baggett, B.,** and **Halla, M.:** Biochem. & Biophys. Acta, **30,** 435, 1958.

(60) **Fieser, L. F.,** and **Fieser, M.:** Natural Products Related to Phenanthrene. New York: Reinhold Publishing Corp., 1949. (61) **Fisher, J. J.:** Obst. & Gynec. Survey, **9,** 479, 1954. (62) **Folch-Pi, J.:** Linkages Between Proteins and Lipids in Blood Cells and Plasma Proteins, Their State in Nature, New York: Academic Press Inc., 1953. **Furuhjelm, M.,** and **Waller, R.:** Acta Endocrinol., **27,** 482, 1958.

(64) **Goldzieher, M. A.:** J. Clin. Endocrinol. & Metab., **16,** 249, 1956. (65) **Goldzieher, J. W., Baker, R. E.,** and **Nyman, M. A.:** Endocrinology, **65,** 310, 1959. (66) **Gooden,**

E. E., and **Villee, C. A.**: Ibid., **58**, 150, 1956. (**67**) **Gray, C. L.**, and **Bischoff, F.**: Am. J. Physiol., **180**, 279, 1955. (**68**) **Greene, R. R., Roddick, J. W., Jr.**, and **Milligan, M.**: Ann. New York Acad. Sci., **75**, 586, 1958.

(69) **Hagerman, D. D.**, and **Villee, C. A.**: J. Biol. Chem., **234**, 2031, 1959. (**70**) **Hagopian, M.**, and **Levy, L. K.**: Biochem. & Biophys. Acta, **30**, 641, 1958. (**71**) **Herrmann, W. L., Schmindl, I.**, and **Bandy, P. K.**: Abstracts of 41st Meeting of the Endocrine Society, 1959. (**72**) **Hollander, N.**, and **Hollander, V. P.**: J. Biol. Chem., **233**, 1097, 1958. (**73**) **Hollander, N., Brown, J. P.**, and **Hollander, V. P.**: Abstracts of 41st Meeting of the Endocrine Society, 1959. (**74**) **Hollander, V. P.**: J. Clin. Invest., **38**, 1012, 1959. (**75**) **Hollander, V. P.**, and **Stephen, M. L.**: J. Biol. Chem., **234**, 1901, 1959. (**76**) **Huffman, M., MacCouquodale, D., Thayer, S. A., Doisy, E. A., Smith, G. V.**, and **Smith, O. W.**: Ibid., **134**, 591, 1940. (**77**) **Huggins, C.**, and **Jensen, E. V.**: J. Exper. Med., **102**, 335, 1955. (**78**) **Hurlock, B.**, and **Talalay, P.**: J. Biol. Chem., **227**, 37, 1957.

(79) **Ingle, D. J.**: Proc. Soc. Exper. Biol. & Med., **100**, 439, 1959. (**80**) **Ittrich, G.**: Ztschr. f. physiol., **312**, 1, 1958.

(81) **Jones, G. E. S.**: The Management of Endocrine Disorders of Menstruation and Fertility. Springfield, Ill.: Charles C Thomas, 1954. (**82**) **Jones, H.**, and **Jones, G. E. S.**: Obst. & Gynec. Survey, **13**, 536, 1958.

(83) **Keller, M.**: J. Clin. Endocrinol. & Metab., **16**, 1075, 1956. (**84**) **Kinsella, R. A., Jr., Francis, F. E., Thayer, S. A.**, and **Doisy, E. A.**: J. Biol. Chem., **219**, 265, 1956. (**85**) **Kraychy, S.**, and **Gallagher, T. F.**: J. Am. Chem. Soc., **79**, 754, 1957. (**86**) Iidem: J. Biol. Chem., **229**, 519, 1957.

(87) **Landau, R. L., Bergenstal, D. M., Lugibihe, L., Dimick, D. F.**, and **Rashid, E.**: J. Clin. Endocrinol. & Metab., **17**, 177, 1957. (**88**) **Layne, D. S.**, and **Marrian, C. F.**: Biochem. J., **70**, 244, 1958. (**89**) **Levitz, M., Condon, G. P.**, and **Dancis, J.**: Endocrinology, **58**, 376, 1956. (**90**) **Levitz, M., Spitzer, J. R.**, and **Twombly, G. H.**: J. Biol. Chem., **222**, 981, 1956. (**91**) **Levitz, M., Condon, G. P., Money, W. L.**, and **Dancis, J.**: Fed. Proc., **18**, 1079, 1959. (**92**) **Levy, R. H.**, and **Talalay, P.**: J. Biol. Chem., **234**, 209, 1959. (**93**) **Lieberman, S.**, and **Teich, S.**: Pharacol. Rev., **5**, 285, 1953. (**94**) **Loke, K. H., Marrian, G. F., Johnson, W. S., Meyer, W. L.**, and **Cameron, D. D.**: Biochem. & Biophys. Acta, **28**, 214, 1958. (**95**) **Loraine, J. A.**: The Clinical Application of Hormone Assay. Baltimore: The Willams & Wilkins Co., p. 154, 1957. (**96**) Idem: Ibid., p. 155. (**97**) Idem: Ibid., p. 172. (**98**) Idem: Ibid., p. 201.

(99) **McBride, J. M.**: J. Clin. Endocrinol. & Metab., **17**, 1440, 1957. (**100**) **Marrian, G. F.**: Biochem. J., **24**, 1021, 1930. (**101**) **Marrian, G. F.**, and **Bauld, W. S.**: Ibid., **59**, 136, 1955. (**102**) **Marrian, G. F., Loke, K. H., Watson, E. J. D.**, and **Panattoni, M.**: Biochem. J., **66**, 60, 1957. (**103**) **Marrian, G. F.**: Cancer, **10**, 704, 1957. (**104**) **Merrill, R. C.**: Phys. Rev., **38**, 463, 1958. (**105**) **Migeon, C. J.**: J. Clin. Endocrinol., **13**, 674, 1953. (**106**) **Migeon, C. J., Sandberg, A. A., Decker, H. A., Smith, D. F.**, and **Paul, A. C.**: J. Clin. Endocrinol. & Metab., **16**, 1137, 1956. (**107**) **Migeon, C. J., Sandberg, A. A., Paul, A. C.**, and **Samuels, L. T.**: Ibid., **16**, 1291, 1956. (**108**) **Migeon, C. J., Wall, P. E.**, and **Bertrand, J.**: J. Clin. Invest., **38**, 619, 1959. (**109**) **Mitchell, F. L.**, and **Davis, R. E.**: Biochem. J., **56**, 690, 1954. (**110**) **Mueller, G. C.**, and **Rumney, G.**: J. Am. Chem. Soc., **79**, 1004, 1957.

(111) **Nakao, T.**, and **Aizawa, Y.**: Endocrinol. Japan, **3**, 92, 1956. (**112**) **Nyman, M. A., Geiger, J.**, and **Goldziehr, J. U.**: J. Biol. Chem., **234**, 16, 1959.

(113) **Oertel, G. W., West, C. D.**, and **Eik-Nes, G.**: Abstracts of 41st Meeting of the Endocrine Society, 1959.

(114) **Paschkis, K. E.**, and **Rakoff, A. E.**: Recent Progr. Hormone Res., **5**, 115, 1950. (**115**) **Paulsen, C. A., Leach, R. G., Sandberg, H., Sheinfeld, S.**, and **Maddock, W. O.**: J. Am. Geriat. Soc., **6**, 803, 1958. (**116**) **Pearlman, W. H., Pearlman, M. A. J.**, and **Rakoff, A. E.**: J. Biol. Chem., **209**, 803, 1954. (**117**) **Preedy, J. R. K.**, and **Aitken, E. H.**: Lancet, **1**, 191, 1957. (**118**) **Puck, A.**: Klin. Wchnschr., **33**, 865, 1955. (**119**) **Puck, A.**, and **Hubner, K. A.**: Acta endocrinol., **22**, 191, 1956. (**120**) **Puck, A., Korte, W.**, and **Hubner, K. A.**: Deutsch. med. Wchnschr., **82**, 1864, 1957. (**121**) **Puck, A.**: Klin. Wchnschr., **35**, 808, 1957. (**122**) Idem: München. med. Wchnschr., **99**, 1505, 1957. (**123**) **Purdy, R. H., Engel, L. L.**, and **Oncley, J. L.**: Fed. Proc., **18**, 305, 1959.

(124) **Rakoff, A. E.:** Am. J. Obst. & Gynec., **38**, 371, 1939. (125) **Rakoff, A. E., Paschkis, K. E.,** and **Cantarow, A.:** Ibid., **46**, 856, 1943. (126) **Riley, G. M.:** Gynecologic Endocrinology. New York: Paul B. Hoeber, Inc., 1959. (127) **Roberts, S.,** and **Szego, C. M.:** Annual Review of Biochemistry. Palo Alto, California: Annual Reviews Inc., **24**, 543, 1955. (128) Iidem: Endocrinology, **39**, 183, 1946. (129) **Rosa, C. G.,** and **Velardo, J. T.:** Ann. New York Acad. Sci., **75**, 491, 1959. (130) **Roy, E.,** and **Brown, J. B.:** Ciba Foundation Colloquia on Endocrinology (in discussion). Boston: Little, Brown and Co., **11**, 335, 1957. (131) **Ryan, K.,** and **Engel, L. L.:** Endocrinology, **52**, 287, 1953. (132) **Ryan, K.:** Endocrinology, **63**, 392, 1958. (133) Idem: J. Biol. Chem., **234**, 268, 1959. (134) Idem: Ibid., **234**, 2006, 1959.

(135) **Sandberg, A. A.,** and **Slaunwhite, W. R.:** J. Clin. Endocrinol. & Metab., **16**, 923, 1956. (136) **Sandberg, A. A.,** and **Slaunwhite, W. R.:** J. Clin. Invest., **35**, 1331, 1956. (137) **Sandberg, A. A., Slaunwhite, W. R.,** and **Antoniade, H. N.:** Rec. Prog. in Hor. Res., **13**, 209, 1957. (138) **Sandberg, A. A.,** and **Slaunwhite, W. R.:** J. Clin. Invest., **36**, 1266, 1957. (139) Iidem: Ibid., **38**, 1290, 1959. (140) **Sandberg, A. A., Bacs, N., Schubarg, J. G.,** and **Slaunwhite, W. R.:** Endocrinology, **64**, 775, 1959. (141) **Sandberg, H., Paulsen, C. A., Leach, R. B.,** and **Maddock, W. O.:** J. Clin. Endocrinol. & Metab., **18**, 1268, 1958. (142) **Serchi, G.,** and **Poggi, A. R.:** Chimica., **8**, 9, 1953. (143) **Slaunwhite, W. R., Engel, L. L., Scott, J. F.,** and **Ham, C. L.:** J. Biol. Chem., **201**, 615, 1953. (144) **Slaunwhite, W. R.,** and **Sandberg, A. A.:** Arch. Biochem., **63**, 478, 1956. (145) Iidem: J. Clin. Invest., **38**, 384, 1959. (146) Iidem: Proc. Soc. Exper. Biol. & Med., **101**, 544, 1959. (147) **Smith, G. V., Smith, O. W., Huffman, M. M., Thayer, S. A., MacCouquodale, D. W.,** and **Doisy, E. A.:** J. Biol. Chem., **130**, 431, 1939. (148) **Smith, O. W.,** and **Smith, G. V.:** Rec. Prog. in Hor. Res., **7**, 209, 1952. (149) **Smith, O. W.,** and **Blackham, N. N.:** Acta endocrinol., **28**, 479, 1958. (150) **Smith, O. W.,** and **Smith, G. V.:** Ibid., **28**, 479, 1958. (151) **Smith, O. W.:** Presented at the 82nd Annual Meeting of the American Gynecological Society, 1959. (152) **Snaith, A. H.:** J. Clin. Endocrinol., **18**, 318, 1958. (153) **Stimmel, B. F.:** J. Biol. Chem., **162**, 99, 1946. (154) **Stimmel, B. F., Grollman, A.,** and **Huffman, M. N.:** Ibid., **176**, 461, 1948. (155) **Stimmel, B. F.:** Abstracts of 40th Meeting of Endocrine Society, 1958. (156) **Straw, R. F., Katzman, P. A.,** and **Doisy, E. A.:** Endocrinology, **57**, 87, 1955.

(157) **Taylor, E. S., Bruns, P. D., Hepner, H. J.,** and **Drose, V. E.:** Am. J. Obst. & Gynec., **76**, 987, 1958. (158) **Touchstone, J. C.,** and **Greene, J. W., Jr.:** Abstracts of 41st Meeting of the Endocrine Society, 1959. (159) **Troen, P.:** Ibid. (160) **Troen, P.,** and **Gordon, E. E.:** J. Clin. Invest., **37**, 1516, 1959. (161) **Troen, P.:** Ibid., **38**, 1048, 1959.

(162) **Varangot, J., Suman, A.,** and **Cedard, L.:** Compt. rend. Soc. biol., **150**, 923, 1956. (163) **Velardo, J. T.:** Fert. & Ster., **9**, 479, 1958. (164) Idem: Ann. New York Acad. Sci., **75**, 441, 1959. (165) **Veldhuis, A. H.:** J. Biol. Chem., **202**, 107, 1953. (166) **Villee, C. A.:** Fert. & Ster., **8**, 156, 1957. (167) **Villee, C. A., Hagerman, D. D.,** and **Spencer, A. B.:** Abstracts of 41st Meeting of the Endocrine Society, 1959. (168) **Villee, C. A.:** Ann. New York Acad. Sci., **75**, 524, 1959. (169) **Villee, D. B., Engel, L. L.,** and **Villee, C. A.:** Endocrinology, **65**, 465, 1959.

170) **Wall, P. E.,** and **Migeon, C. J.:** J. Clin. Invest., **38**, 611, 1959. (171) **Watson, E. J.,** and **Marrian, G. F.:** Biochem. J., **63**, 64, 1956. (172) **Werbin, H., Plotz, J., Le Roy, G. V.,** and **Davis, M. E.:** J. Am. Chem. Soc., **79**, 1012, 1957. (173) **Werthessen, N. T.:** Science, **117**, 380, 1953. (174) **West, C. D., Damast, B.,** and **Peassor, O. H.:** J. Clin. Invest., **37**, 341, 1958. (175) **Wiele, R. L. V.,** and **Jailer, J. W.:** Ann. New York Acad. Sci., **75**, 889, 1959. (176) **Wotiz, H. H., Davis, J. W., Lemon, H. M.,** and **Gut, M.:** J. Biol. Chem., **222**, 487, 1956.

(177) **Zondek, B.,** and **Goldberg, S.:** J. Obst. & Gynec. Brit. Emp., **64**, 1, 1957. (178) **Zondek, B.:** Fert. and Ster., **10**, 1, 1959.

BOOK REVIEWS AND NOTICES

L'Heredite en Ophthalmologie. By Jules Francois, Professeur de clinique ophthalmologique a L'Universite de Gand. Pp. 876; 629 ills. Paris: Masson et Cie, 1958. Price, 8,000 fr.

A growing interest in the genetic implications of a large number of ocular diseases is reflected in this ambitious and comprehensive textbook by an ophthalmologist with a broad experience in this field. The importance of the study of genetics in ophthalmology is emphasized by the fact that at least 246 pathologic genes have now been recognized, which are manifested by ocular anomalies, either isolated or in association with other disturbances.

The text is introduced by a brief review of the fundamental principles and recent advances in the science of genetics. A second section reviews the clinical varieties of diseases with an hereditary basis, including a discussion of congenital anomalies, abiotrophies, phakomatoses, malignant tumors, endocrine diseases, metabolic disturbances, functional anomalies and syndromes. A chapter, which will be particularly helpful to the practitioner, lists the mode of transmission of a large number of hereditary diseases, and outlines a method for answering questions on eugenics frequently asked by afflicted patients.

The remainder of the volume is occupied by a systematic and detailed description of the many known hereditary diseases of the eyes and of the systemic diseases having ocular manifestations. This portion of the book should be a useful reference. W.F.

Group Processes; Transactions of Fourth Conference, October, 1957. Edited by Bertram Schaffner, M.D., Columbia University. Pp. 266. New York: Josiah Macy, Jr. Foundation, 1959. Price, $4.50.

The book is a nearly verbatim account of the transactions of the fourth conference discussing group processes. The discussants include not only many of the most qualified scientists but some of the most interesting from the fields of biology, psychology, sociology, anthropology, psychiatry, neurology and communications. In the first two sessions papers by Fritz Redl, the child psychologist, on game ingredients in children's play and on the relationship of these findings to current models of personality were discussed. Redl's essential point was that many current theories cannot explain certain phenomena because they do not have an interactional viewpoint.

Alex Bevelas presented the results of studies on group problem solving and the communication of solutions in groups of businessmen.

Konrad Lorenz offered observations on "The Role of Aggression in Group Formation" derived from observing group behavior of animals in their natural ecology. The group discussed the possibilities of extrapolating these findings to human groups.

The reviewer found the book highly informative and interesting though a little more speculative than in former years. A.S.

La Corticothérapie Surrénale dans le Traitement de le Tuberculose. By C. Gernez-Rieux, H. Warembourg and M. Pauchant. Pp. 216; 35 ills. Paris: Masson et Cie, 1958. Price, 2.600 fr.

After a brief review of the historical development of steroid therapy due emphasis is placed upon the risks inherent in this treatment and the necessity for rigorous control and the concomitant use of antimicrobials in such treatment of all tuberculous manifestations. On the basis of experimental studies and clinical experience explicit rules for safe steroid therapy are laid down. There follow chapters on the treatment of tuberculosis of the serous membranes, miliary and acute pulmonary tuberculosis, chronic pulmonary tuberculosis, endobronchial tuberculosis and primary tuberculosis, with the indications for steroid therapy in each. In tuberculous meningitis the early use of steroids with antimicrobials is advocated in all severe infantile and all adult cases. There are discussions of the use of corticosteroids to combat drug sensitivity and the suprarenal insufficiency following surgery. Various forms of nonpulmonary tuberculosis including Addison's Disease are covered. The physiopathologic study is not as clear as the clinical parts which are well summarized in the final chapter. The bibliography is extensive, covering the French and American literature thoroughly, but contains only four references in German (3 of these Swiss). The illustrating roentgenograms are excellent. Like all French monographs this

topical and useful book has a long table of contents at its end where an index would be more valuable. J.W.

TRANSACTIONS OF THE FIFTH ANNUAL MEETING OF THE ACADEMY OF PSYCHOSOMATIC MEDICINE. THE PSYCHOSOMATIC ASPECTS OF INTERNAL MEDICINE. Edited by WILFRED DORFMAN, M.D., F.A.C.P. Pp. 268. (Paperbacked, Multigraphed.) New York: The Academy of Psychosomatic Medicine, 1959.

THE editor, at present the President-elect of the Academy of Psychosomatic Medicine, has compiled summaries and abstracts of papers presented by 78 speakers at the annual meeting of the Academy in New York City in October, 1958. Some authors, such as Weiss, Deutsch, Wittkower, Rosenbaum and Abramson, have long been active as leaders of psychosomatic thinking. Other authors, both psychiatric and nonpsychiatric, are more recent students of the field.

The subject matter touches on aspects of psychophysiology, a wide variety of so-called psychosomatic problems, and psychiatric and psychotherapeutic interests. In addition there is a symposium on Mental Health and the General Physician.

The papers aim usually at a clinical level and there is a great emphasis on mind and body correlations. There is a little of something for everybody who is interested in the field of psychosomatic medicine. The mean level would probably direct toward the clinician who has been in medical practice as a nonpsychiatrist and who is now becoming interested in psychosomatic correlations. H.F.

COLLECTED PAPERS. BY SIGMUND FREUD, M.D. First American Edition (previous edition printed in London). Pp. 2274. New York: Basic Books Inc., 1959. Price, $25.00 the set.

THESE collected papers of Sigmund Freud, first published in 1924, have remained essential textbooks to the student of psychoanalysis. Over the years their value as a contribution to the understanding of human behavior has increased.

Volume I deals primarily with early papers (1893–1905) and a history of the psychoanalytic movement. Volume II deals with clinical papers and papers on technique. Volume III is devoted to Freud's famous case histories. Volume IV covers papers on metapsychology and papers on applied psychoanalysis. Volume V deals with miscellaneous papers written 1888 to 1938.

These papers of Freud are classical writings in psychoanalysis and will remain a basic study for students of the subject. It is most fortunate that these papers are now more available with their first publication in this country. These books will interest all people interested in human behavior. The analyst and student analyst however, might be well advised to consider the purchase of the more extensive writing "The Complete Psychological Works of Sigmund Freud." Here certain commentaries have been added not included in the Collected Papers. M.B.

TREATMENT OF BREAST TUMORS. BY ROBERT S. POLLACK, M.D., Clinical Instructor in Surgery, Stanford University School of Medicine. Pp. 147; 63 ills. Philadelphia: Lea & Febiger, 1958. Price, $6.00.

THIS is an excellent monograph on the diagnosis and management of breast tumors, with particular emphasis on cancer of the breast. In addition to the operations designed to eradicate the primary lesion, there is also given due consideration to radiation therapy, oophorectomy, adrenalectomy, hypophysectomy, and the adjunct use of hormones and chemotherapy for metastatic stages of the disease.

The illustrations are numerous and are clearly reproduced on the fine quality paper which is used throughout the text. This volume contains in concise form much information that should be helpful in dealing with the many problems associated with the treatment of breast tumors. C.Z.

ADVANCES IN PROTEIN CHEMISTRY, VOL. XII. Edited by C. B. ANFINSEN, JR., M. L. ANSON, KENNETH BAILEY AND JOHN T. EDSALL. Pp. 687; 111 ills. New York: Academic Press, Inc., 1957. Price, $14.00.

THIS volume consists of a series of articles which deal with recent major advances in protein chemistry. Included are discussions of The Fibrinogen-Fibrin Conversion; X-ray Analysis and Protein Structure; The Human Hemoglobins: Their Properties and Genetic Control; Hormones of the Anterior Pituitary Gland; The Melanocyte-Stimulating and Lactogenic Hormones; The Activation of Zymogens; The Chemical Nature of Antibodies; and The Synthesis of Peptides. All of the

contributors are authorities in their respective fields.

Workers in these and related areas will find much of interest in this as in preceding volumes of this important review series.

C.Z.

BIOCHEMICAL DISORDERS IN HUMAN DISEASE. Edited by R. H. S. Thompson, M.A., D.M., Professor of Chemical Pathology, University of London and E. J. KING, PH.D., D.SC., F.R.I.C., Professor of Chemical Pathology, University of London. Pp. 843; 121 ills. New York: Academic Press, Inc., 1957. Price, $12.60.

DURING recent years, rapid strides in biochemical theory and techniques have greatly extended the realm of diseases which are interpretable in terms of disordered biochemistry. This book, therefore, was designed to assemble, relate, and interpret advances in knowledge of biochemical disturbances associated with human disease. Intended primarily for medical readers, the material is presented with the aim of showing how various diseases of a given organ-system are dependent on disorders of enzyme-catalysed reactions which occur within cells. Thus, diseases of the gastrointestinal tract, the liver, the blood and its clotting mechanism, the kidney, the nervous system, and so on are discussed from this point of view.

The editors and the respective contributors are to be congratulated on the production of a highly readable, lucid, and competent treatise. Present day physicians will gain not only a fuller understanding of the pathogenesis of many diseases, but also much of practical importance in the diagnosis and management of both medical and surgical patients.

C.Z.

BIOSYNTHESIS OF TERPENES AND STEROLS. Ciba Foundation Symposium. Edited by G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B.; B.CH., AND CECILIA M. O'CONNOR, B.SC. Pp. 311; 102 ills. Boston: Little, Brown & Co., 1959. Price, $8.75.

THIS volume contains the proceedings of a symposium held in May, 1958, under the auspices of the Ciba Foundation. Included are excellent discussions dealing with the biogenesis and transformation of squalene, the discovery and elucidation of meralonic acid, alterations of cholesterol biosynthesis in liver cell fractions under various experimental conditions, the formation and metabolism of bile acids, and many other equally important facets of terpene and sterol metabolism. Biochemists, clinical investigators, and others concerned with the basic biochemical, physiologic, and clinical implications of lipid metabolism will find this a valuable and stimulating group of papers.

C.Z.

SURGERY OF THE SYMPATHETIC NERVOUS SYSTEM. BY SIR JAMES PATERSON ROSS, K.C.V.O., LL.D., M.S., St. Bartholomew's Hospital, London (Surgical Professorial Unit). 3rd ed. Pp. 166; 19 ills. London: Bailliere, Tindall and Cox, 1958 (The Williams & Wilkins Co., Baltimore, U.S. Agents). Price, $8.00.

THIS book deals with surgery of the sympathetic nervous system and does not include consideration of the entire autonomic system. It is divided into six sections, which cover anatomy and physiology; peripheral circulation, arterial hypertension; hyperhidrosis, causalgia, and visceral pain.

The text is well written and well illustrated with photographs, X-ray plates, and diagrams.

The only adverse criticism might be that the bibliography is not quite as large as one would like for such an authoritative work. On the whole, this book is recommended to surgeons interested in any of the entities for which sympathectomy might be indicated.

R.B.

THE INVESTIGATION OF THE RELATIVE FUNCTION OF THE RIGHT AND LEFT LUNG BY BRONCHO-SPIROMETRY. BY FRANK BERGAN, M.D., Oslo City Hospitals. Pp. 142; 85 ills. New York: Grune & Stratton, Inc., 1958. Price, $4.50.

A THOROUGH coverage of the theory and intimate technique of broncho-spirometry, based on the literature and experiences from an important group, are set forth in this volume. Details and suggestions are good. The discussion is valuable and the examples furnished are worthy of consideration. The physiological principles expounded are sound.

M.O.

INSTRUMENTATION IN ANESTHESIOLOGY. BY WILLIAM H. L. DORNETTE, M.D., Professor of Anesthesiology, University of Tennessee College of Medicine and VERNE L. BRECHNER, M.D., Assistant Professor of Anesthesiology, University of California School of Medicine at Los Angeles. Pp. 242; 130 ills.

Philadelphia: Lea & Febiger, 1959. Price, $8.00.

THIS is a valuable book for all anesthesiologists to have in their library because the modern practice of anesthesiology requires instrumentation.

The authors have included in this text a complete but brief description of all the electronic instruments used in anesthesiology. In the sections devoted to the principles of electronics, the authors in an attempt for brevity and simplification permitted a few small inaccuracies to occur. This, however, does not detract from the value of this book.

The section on methods of gas analysis is complete in every detail. The same can be said of the chapters dealing with cardiac monitoring, electroencephalography, thermometry, manometry and flowmometry.

The authors were also able to provide practical information concerning various instruments. This will enable anesthesiologists to select the proper instrument for a specific purpose.

This textbook should be a must for all residents in anesthesiology. L.K.

MUIR'S TEXTBOOK OF PATHOLOGY. Revised by D. F. CAPPELL, C.B.E., M.D., F.R.F.P.S., M.R.C.P., F.R.S. ED., Professor of Pathology, University of Glasgow. 7th ed. Pp. 1201; 733 ills. London: Edward Arnold, Ltd., 1958 (The Williams & Wilkins Co., Baltimore, exclusive U.S. agents). Price, $14.50.

THIS textbook follows the pattern of previous editions established by Sir Robert Muir. The author has relied primarily on his own personal experiences and interpretations so that the bibliography is only a matter of 3 pages. The introduction is very beautifully handled and gives a clear and concise resume of the causes of disease and of the subsequent tissue reactions. The remaining chapters follow the usual format of textbooks of pathology, taking up first the circulatory disturbances, inflammation, and others and then special organ pathology. The text is very well written and gives a clear portrayal of morbid conditions. It is complete and up-to-date mentioning as one example, the Zollinger-Ellison syndrome. The illustrations have been carefully selected; they are clear-cut and demonstrate adequately both the gross and microscopic features of the lesions which they represent. The type is easy to read and each chapter has been given its appropriate heading and sub-headings. This book is a valuable addition to our present texts on pathology. A.P.

THE UTERUS (Ann. of the New York Acad. of Sci., Vol. 75, Art. 2). BY JOSEPH T. VELARDO AND 74 OTHERS. Pp. 655; illustrated. New York: New York Academy of Sciences, 1959. Price, $7.00.

THIS issue of the Annals of the New York Academy of Sciences is a 655 page paperbound publication of the material presented during an Academy-sponsored symposium devoted to the uterus. The authors are for the most part authorities on the subject they discuss and while some of the papers are reviews of work previously done much new material is included.

The material related to the uterus is divided into 7 categories in each of which from 2 to 5 reports are included. The divisions include, I) Historical and Morphogenetic Considerations, II) Biochemistry and Histochemistry of the Uterus, III) Problems in Uterine Tumors, IV) Blood Coagulation During Pregnancy, Labor and Puerperium, V) Aspects of Gravid Uterus, VI) Uterine Contractions, VII) Menstruation and Menstrual Disorders. In addition the Structural and Functional Aspects of the Placenta and Nonsteroidal Ovarian Hormones are discussed.

The papers are well illustrated with line drawings, photographs, photomicrographs, tables, graphs and charts and most are extensively annotated with inclusive bibliographies, The only published discussions are those related to the papers on nonsteroidal ovarian hormones.

This is a valuable compilation of information for anyone who is interested in the uterus. While much of the material is related more to investigation rather than to clinical practice, many of the papers contain information which is both useful and important to the clinician and which he can put to good use in his daily work. J.W.

THIRD SYMPOSIUM ON REPRODUCTION AND INFERTILITY. Edited by F. X. GASSNER, Colorado State University. Pp. 273; illustrated. New York, London, Paris, Los Angeles: Pergamon Press, Inc. 1958. Price, $6.50.

MOST physicians profess envy for veterinarians because the problems involved in caring for animals appear to be so much simpler than those with human beings. If the Proceedings of the Third Symposium on Reproduction and Infertility held at the Colorado

State University is an indication of veterinary practice, however, human and animal gynecology is not dissimilar. The titles of many of the papers are completely familiar to physicians who attend meetings devoted to human fertility, namely, Neoplasms of the Genitalia of the Bovine, Recent Studies on the Mechanism of Ovulation in the Cow, Biosynthesis of Steroid Hormones, Estrogen Determination in Blood and Body Fluids of Cattle, Estrogenic Steroids in Swine Pregnancy Urine, to mention a few.

It is of great interest to compare certain animal disorders with those encountered in women; for instance of 186 neoplasms discovered during the slaughtering of cattle 44, or 24%, involved the female genital organs. Of these 26 were adenocarcinoma of the uterus, 4 leiomyomas, 6 uterine lymphosarcomas, 1 ovarian cystadenocarcinoma, 6 granulosa cell tumors and 1 squamous cell carcinoma of the vulva. No tumors of the cervix and vagina were encountered. Endocrine problems are also similar. A round table discussion in the use of frozen semen for artificial insemination in cattle is excellent.

While there is only one paper, "The Maintenance of Human Pregnancy with Progestational Compounds," which would interest the practicing physician there is a wealth of material to stimulate those studying fertility and endocrine problems. J.W.

CHLORPROPAMIDE AND DIABETES MELLITUS. Edited by MARTIN G. GOLDNER, Jewish Chronic Disease Hospital, Brooklyn. Pp. 617; 453 ills. New York: New York Academy of Science, 1959. Price, $5.00.

THE re-introduction of oral hypoglycemic agents in the management of diabetes mellitus has fostered an enormous interest and research in the etiology of the disease, mechanisms of insulin action, and the role of liver and other tissues in carbohydrate metabolism. This monograph contains a series of 70 papers providing detailed information on these and related topics with particular reference to chlorpropamide, including pharmacologic, metabolic and clinicometabolic studies of this compound. The data concerned with the mechanism of action do not permit precise conclusions; however, there is evidence to indicate that liberation of endogenous insulin is promoted by this compound and that there is also a decrease in gluconeogenesis following its administrations. Clinical trials attest uniformly to its effectiveness in the control of a significant percentage of patients and reveal a greater potency than tolbutamide. Side effects have been observed more frequently than with tolbutamide due, possibly, to the narrow therapeutic range of the compound. These excellent presentations and discussions should be available to all investigators and physicians involved in research or treatment in the field of diabetes mellitus. C.S.

THE CHEMICAL DYNAMICS OF BONE MINERAL. By WILLIAM F. NEUMAN AND MARGARET W. NEUMAN, University of Rochester. Pp. 209; 54 ills. Chicago: University of Chicago Press, 1958. Price, $5.00.

THE authors are chemists and they have written a book for chemists to read. Clinicians and clinical laboratory people with a special background in the physiology of bone tissue will, with considerable effort, be able to understand most of their text. Others might do well to wait for the "movie version."

None of this denigrates the character or value of the book they have produced. These two authors probably know more than any other persons about the chemistry of bone mineralization. Because it is an important subject and because some sort of understanding of its mechanisms is a prerequisite for an understanding of bone disease, this little volume is an extremely valuable contribution. Because it is an authentic source reference, its "translation" will eventually seep down to the level of clinical usefulness. E.A.

PATHOLOGY. BY PETER A. HERBUT, M.D., Professor of Pathology, Jefferson Medical College. 2nd ed. Pp. 1516; 1506 ills. Philadelphia: Lea & Febiger, 1959. Price, $18.50.

DR. HERBUT'S text of Pathology which was published in 1955, has been completely revised with the addition of nearly 300 pages and 128 illustrations.

For the past decade there has been a shifting of emphasis in medicine and consequently in the teaching of pathology from the morphology of disease to the physiology of disease. Dr. Herbut has sought to meet the demands of this shift by adding to his originally conventional text a section entitled "Pathologic Physiology," before the discussion of the pathologic anatomy of each major system. For assistance in this matter he has included the contributions of twenty new collaborators.

This edition is certainly a step in the right direction. Since most of us feel that it is

the disease process and not the result of the disease process that we are trying to teach, any assistance in the achievement of this objective is welcome. Dr. Herbut apparently has not yet solved our problem of how to reduce the whole in order to emphasize the important. Adding 300 pages to his text does not help in this respect. E.A.

NOW OR NEVER: THE PROMISE OF THE MIDDLE YEARS. BY SMILEY BLANTON, M.D., with ARTHUR GORDON, Director of the Religo-Psychiatric Clinic of the Marble Collegiate Church. Pp. 273. New York: Prentice-Hall Inc., 1959. Price, $4.95.

THE purpose of this book is to help people in the "middle years" of their lives to understand and solve some of the psychological problems of this period of life. There are chapters on psychodynamics, marriage, teen age children, problems of work, money, the body and physical illness, alcohol, sex, the power of religion, aging parents and facing old age.

The book is well-written and in language readily understandable by the layman. Numerous clinical examples make the general principles clear and believable. The psychiatric and psychoanalytic dynamics put forth in this book are sound.

There remains some question as to whether mental health education of this type can lead to significant personality changes. There are also implications in the book that long-standing personality conflicts can be solved in two or three interviews.

However, the book is thought-provoking and may help some people take stock of themselves and seek to change. In some cases, it may lead to fruitful discussions between husbands and wives.

This book is wholeheartedly recommended for the lay public and the physician, and would also be of interest to many psychiatrists.

M.B.

ACTUALITES BIOCHIMIQUES: ASPECTS ACTUELS DE LA BIOCHIMIE DES ACIDES AMINES ET DES PROTEINES. BY J. T. EDSALL, Harvard University. Pp. 156; 45 ills. Paris: Masson et Cie, 1958. Price, 2.000 fr.

DR. EDSALL delivered a series of 10 lectures while a visiting Professor in France in 1955–56 on the Proteins and Amino Acids. The present paper-bound volume (in French) represents a reorganized (into 7 chapters) version of his lectures. Various chemical and physical properties of amino acids and peptides are described in the first two chapters and a considerable portion of the book is concerned with the structure of peptides and proteins. Of especial interest are the chapters on the properties and characteristics of the serum albumins and mercaptoalbumin.

R.B.

EXPOSES ANNUELS DE BIOCHIMIE MEDICALE, VOLUME 19. Edited by P. BOULANGER (Lille), M. F. JAYLE (Paris), and J. ROCHE (Paris). Pp. 240; 59 ills. Paris: Masson et Cie, 1957. Price, 3.000 fr.

THIS volume included a series of review articles (in French) by European workers on topics of interest to those engaged in medical research. The first 5 papers are concerned with the plasma proteins and include descriptions of Waldenstrom's macroglobulinemias, C-reactive proteins and various other lipoproteins.

Chapter 6, written by Dr. A. C. Frazer of the University of Birmingham is entitled "Stéatorrhée." Dr. Theodore Wieland wrote Chapter 7 concerning the toxic materials in *Amanita phalloides*. Chapter 8 by Dr. Marcel Florkin provides information concerning the amino acid composition of the tissues of various animal species. The last chapters include thermodynamic studies of immunologic reactions and by Dr. Albert Wettstein, "Aldosterone."

R.B.

THE CHEMISTRY AND BIOLOGY OF PURINES (Ciba Foundation Symposium). Edited by G. E. W. WOLSTENHOLME AND C. M. O'CONNOR. Pp. 327; 124 ills. Boston: Little, Brown and Co., 1957. Price, $9.00.

THE papers delivered at a symposium held in England 8–10 May 1957 and the appropriate discussions thereto, provide the subject matter of this volume. The topics include the synthesis and physical properties of naturally-occurring as well as synthetic purine derivatives. Also described is the status of our knowledge of the *in vivo* and *in vitro* synthesis of purine nucleosides and nucleotides. The chemistry and biological effects of potential therapeutic agents such as 6-mercaptopurine, 8-azapurines, puromycin and analogues of vitamin B_{12} are described.

The participants were men who have been actively engaged in research in the field and their papers are marked by their excellence.

This book is recommended highly to those who would like to learn more of the chemistry and potential uses of the very interesting compounds described. It is a "must" for those

whose work and interests touch the field of nucleic acid metabolism. R.B.

SURGICAL PATHOLOGY. BY LAUREN V. ACKERMAN, M.D., Washington University School of Medicine. 2nd ed. Pp. 1096; 1114 ills. St. Louis: C. V. Mobsy Co., 1959. Price, $15.00.

MANY books have appeared in the past with the title of "Surgical Pathology." One gets the impression that most of them represent the product of pathologists who couldn't quite make up their minds to write a complete text in pathology. Dr. Ackerman's book tends to escape this criticism because one finds things here which do not appear or which appear less completely in the texts on the whole subject. This reviewer has never been quite clear just what surgical pathology is. One hears that it is pathology which interests the surgeon but today the surgeon is, or should be, the internist who operates. If he isn't interested in lobar pneumonia he shouldn't be operating in the chest.

Dr. Ackerman has chosen to write on the many aspects of pathology which interest him and so the book is completely authentic since the author is a man of immense experience and ability. A reading of this text will enhance anyone's knowledge of medicine whether he be surgeon, pathologist or internist. The fact that it is an "incomplete" pathology does not subtract from its value, for some areas such as wound healing are more complete than one can find in any general text on the subject. E.A.

AUTOPSY DIAGNOSIS AND TECHNIQUE. BY OTTO SAPHIR, M.D., Michael Reese Hospital. 4th ed. Pp. 549; 80 ills. New York: Paul B. Hoeber, Inc., 1958. Price, $8.50.

OVER the past two decades, this little handbook has become the generally used guide for necropsy procedure. Indeed, so much has been added since its original edition, that, except for its format, the book can scarcely now be considered a handbook. Three new chapters have been added to the present edition; one on the history of the necropsy by Sidney Farber, one concerning necropsies on patients treated with radioactive isotopes and one on tissue banking. This reader is reminded that useful handbooks sometimes become something less useful by growing to textbook size. E.A.

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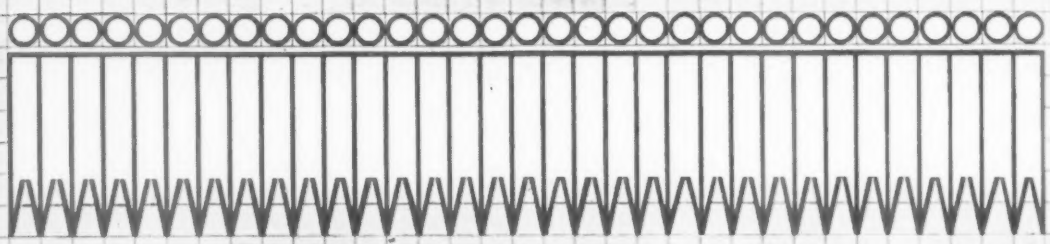

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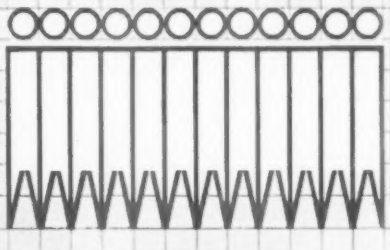

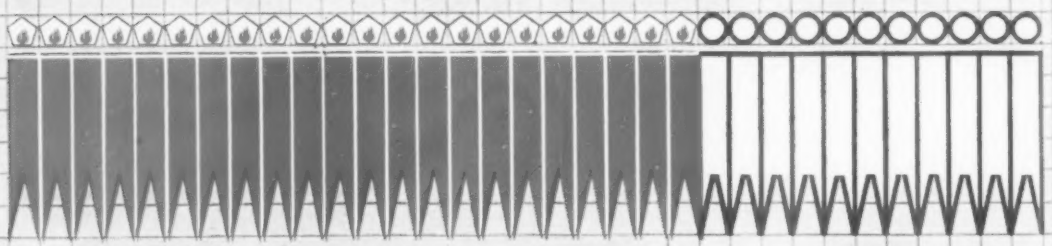

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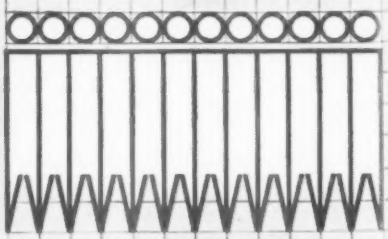

1. Boland, E. W., and Headley, N. E.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.
2. Bunim, J. J., et al.: Paper read before the Am. Rheum. Assoc., San Francisco, Calif., June 21, 1958.

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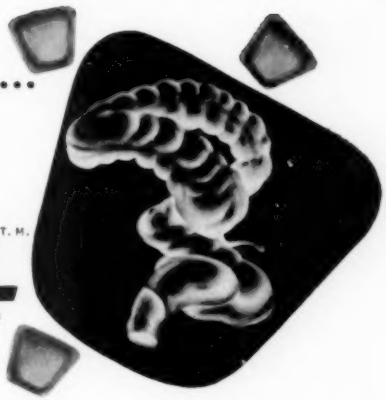

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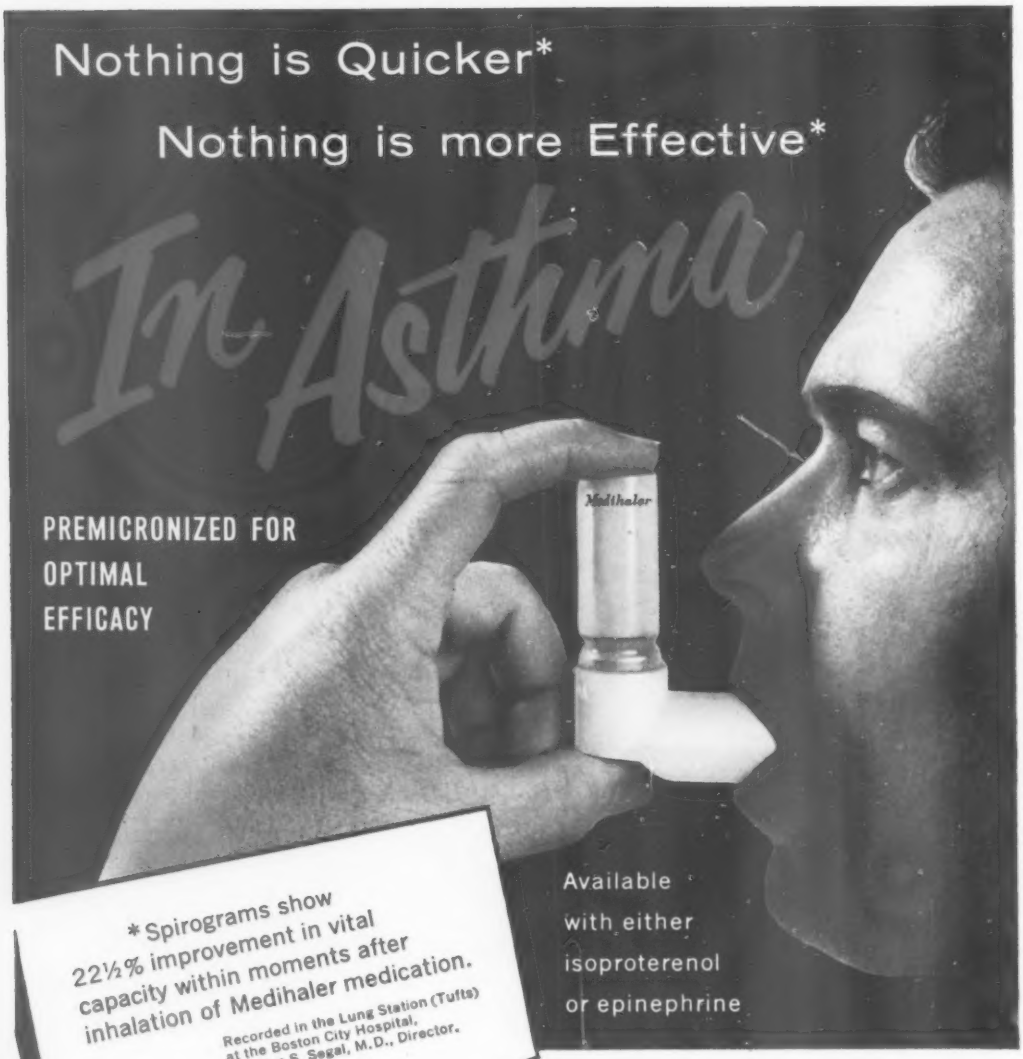

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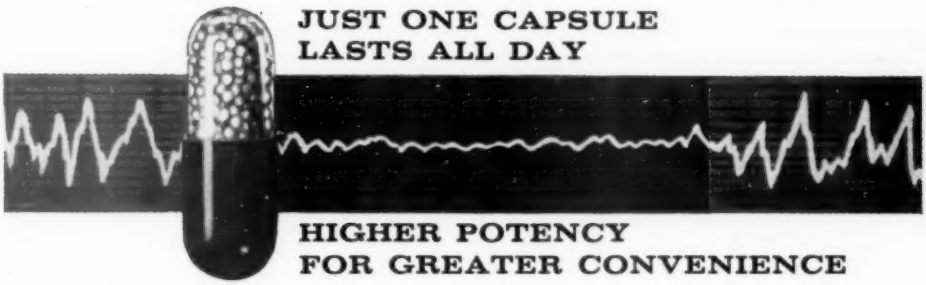

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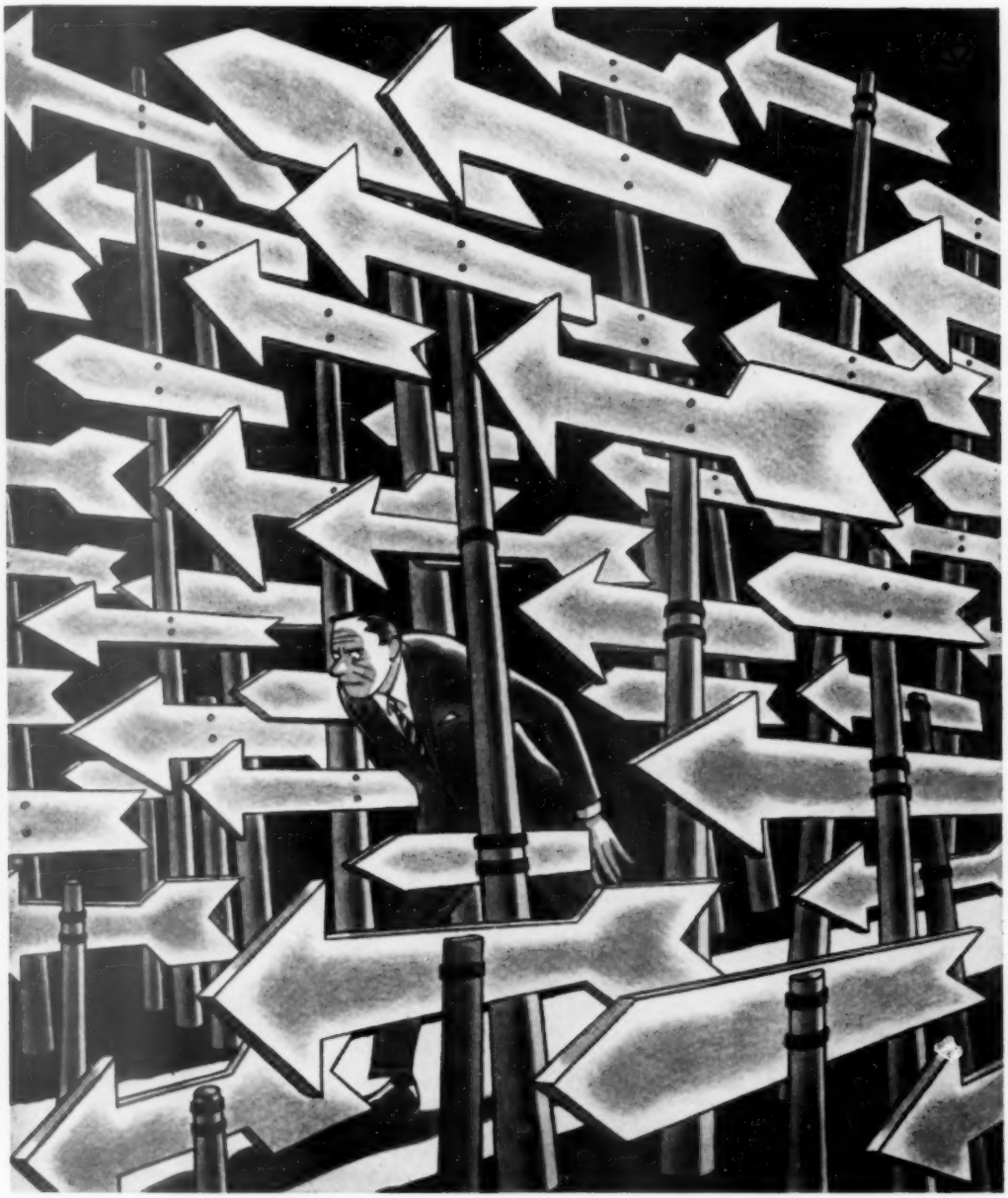

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F. K. Albrecht, Mod. Mgmnt. Clin. Med. P674, Williams & Wilkins.
F. W. Wittich, J. Am. Ger. Soc., 3:239, 1955.

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One capsule and one enteric-coated (delayed action) tablet at night will give your patient a full night's sleep. A capsule, two or three times a day, will complete round-the-clock relief.*

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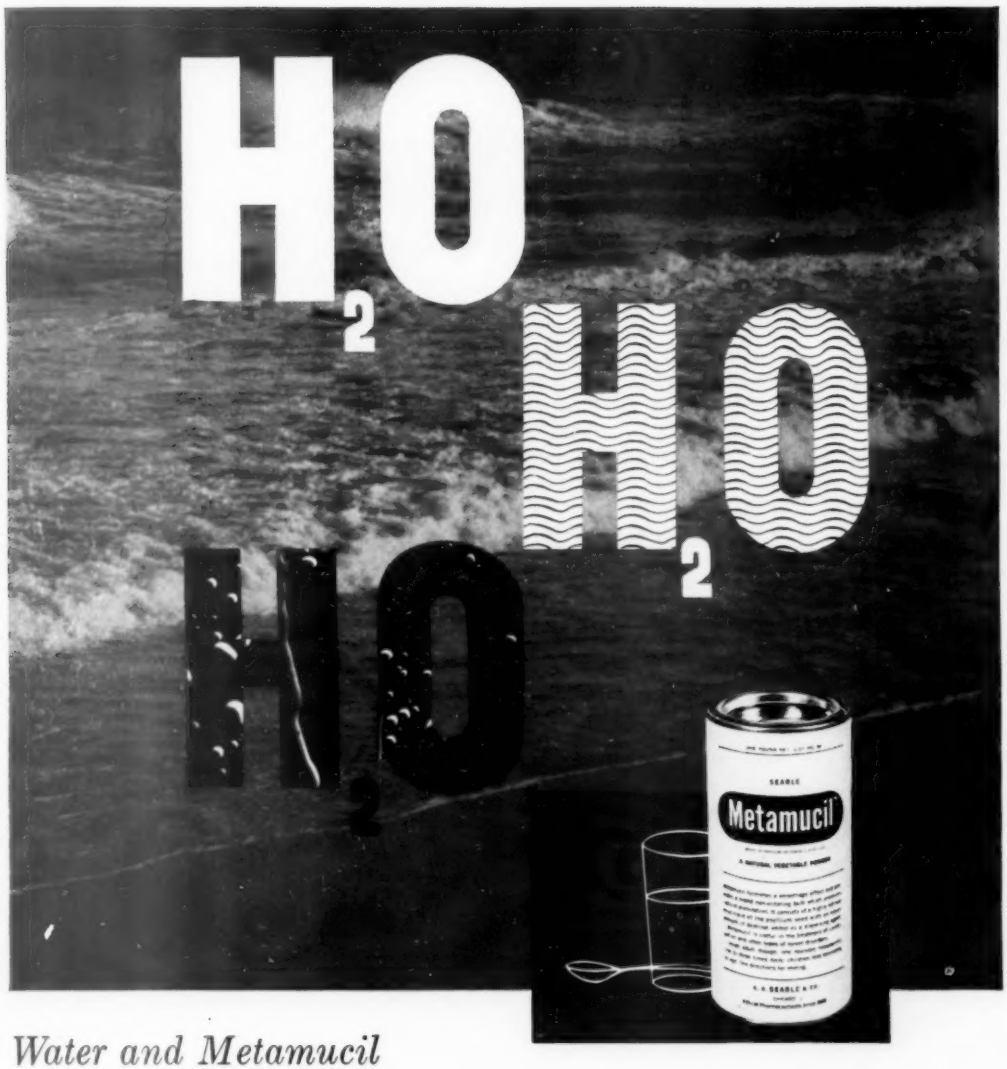

Water and Metamucil

Both are basic for relief and correction of constipation

Effective relief of constipation and actual correction of the condition depend on an intake of a sufficient quantity of water to facilitate movement of the fecal mass in the bowel lumen. Also useful is Metamucil which adds a soft, bland bulk to the bowel contents to stimulate normal peristalsis and also hold water within stools to keep them soft and easy to pass. Thus Metamucil and an adequate water intake induce natural elimination and promote regularity.

Metamucil®

brand of psyllium hydrophilic mucilloid

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(March and September)
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(June and December)—I. J. Wolman and
A. M. Bongiovanni

Gynecology and Obstetrics
(June and December)
C. Bachman and Franklin L. Payne

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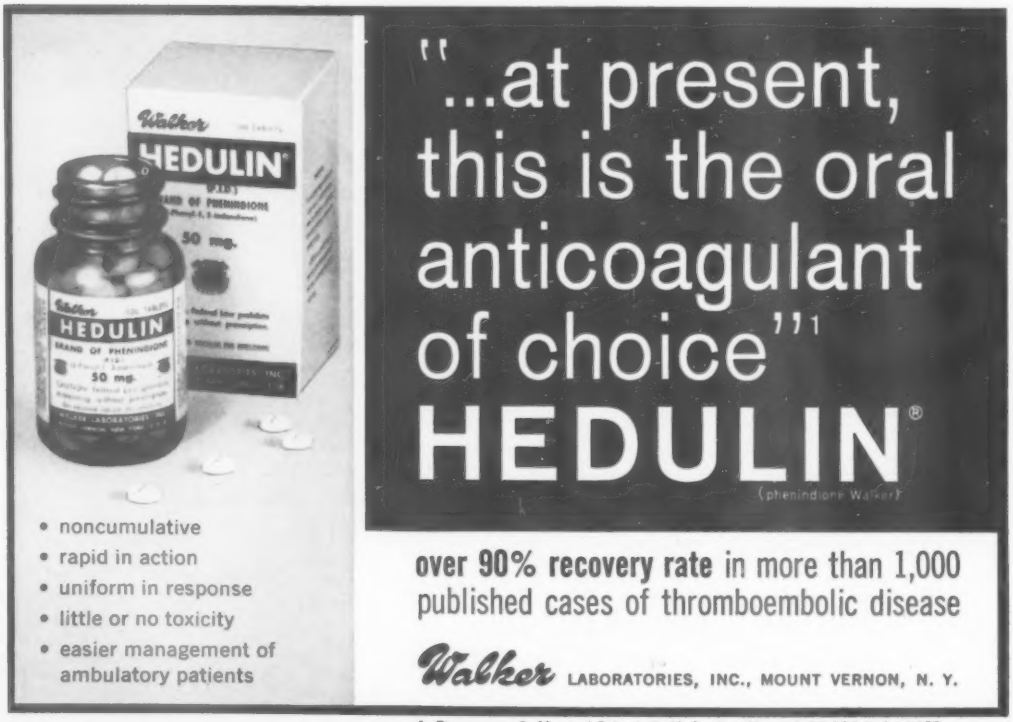
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1. Breneman, G. M., and Priest, E. McC.: Am. Heart J. 50:129 (July) 1955.

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Curbs emotion as it boosts coronary blood supply

CONTROL OF EMOTIONAL EXERTION with Miltrate leaves him more freedom for physical activity.

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Each tablet contains: 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

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WALLACE LABORATORIES · *New Brunswick, N. J.*

CML-9159-59 *TRADE-MARK

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CLINICAL NOTES

HEMATOLOGY

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SUPPLIED 5 cc. color-break ampules, boxes of 10

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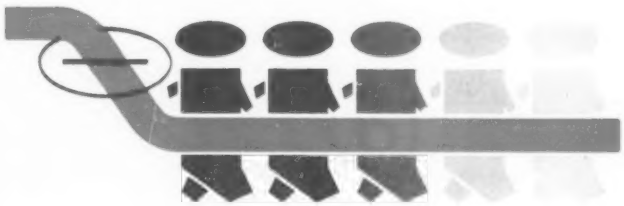

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economical once-a-day dosage

when replacement or reduction of insulin is desirable
when other oral therapy has failed
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The clinical aim, following immediate suppression of disease symptoms, is to maintain the patient symptom-free... with minimal side effects.

The logical course is to select the steroid with the best ratio of desired effects to undesired effects:

the corticosteroid that hits the disease, but spares the patient

Medrol*

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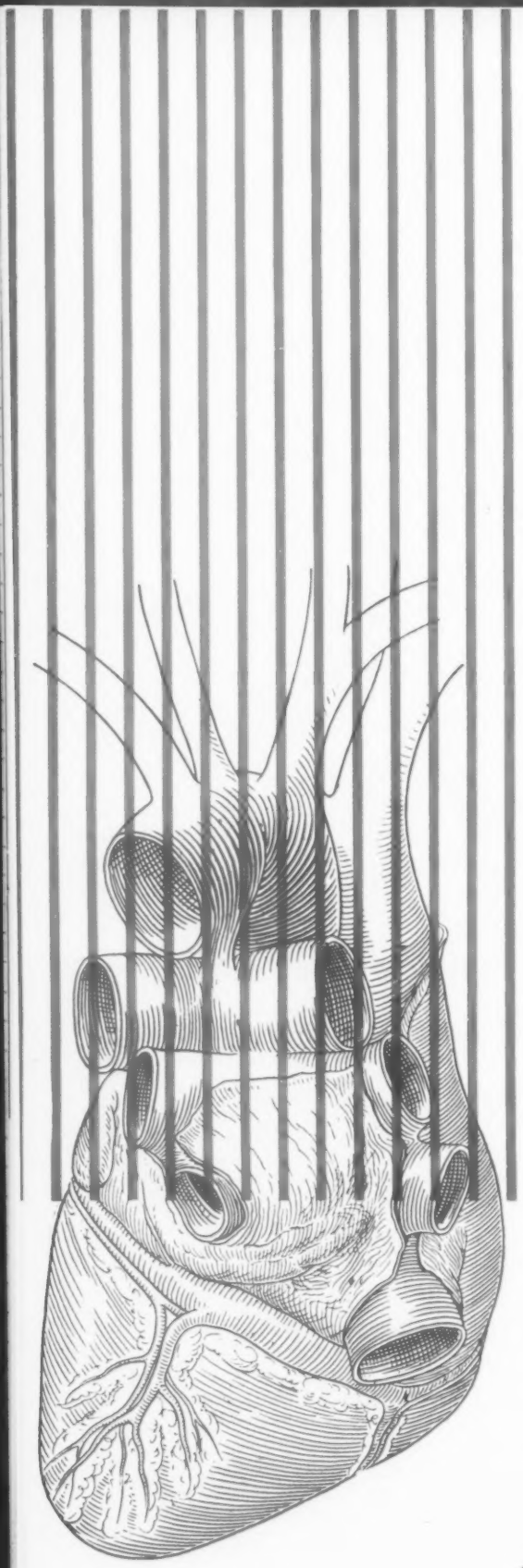
*TRADEMARK, REG. U. S. PAT. OFF.—METHYLPREDNISOLONE, UPJOHN



Now, a single agent, with important clinical indi

for total management of angina pectoris

Marplan prevents pain: Marplan is indicated primarily for patients with moderately severe to intractable angina pectoris. It has demonstrated a high degree of effectiveness. When used on a continuous dosage schedule, Marplan prevents pain, increases exercise tolerance and reduces nitroglycerin requirements.[1-3] To date, Marplan prophylaxis has been evaluated in over 300 angina patients. The response rate was 76 per cent with improvement ranging from a reduction in the number of attacks to virtual abolition of the anginal state.[1] One study reported "excellent effects with relatively small doses" and "greater relief than [with] any other compound in our experience."[2]

Marplan creates a more confident mental climate: Many angina patients display a more cheerful outlook when on Marplan therapy. This mental improvement is undoubtedly due to the antidepressive action of Marplan. However, it should be stressed that Marplan is indicated for *symptomatic* control of angina pectoris and, while it frequently abolishes anginal pain, Marplan does not appear to influence the EKG. Hence, as with previously available prophylactic agents, it is imperative that patients be instructed to maintain the same restriction of activity in force prior to Marplan therapy.

with two distinct primary effects, for two indications

Marplan

a happy balance of potency/safety

A broad clinical research program continues to define the full range of Marplan's clinical applicability. However, already some 300 research clinicians have evaluated Marplan in more than 4000 patients in two primary diagnostic categories—*angina pectoris and depression.*

Marplan has been shown to be considerably more active than other amine oxidase regulators. While clinically such increase in potency has heretofore been associated with increased side effects, Marplan strikes a happy balance of potency/safety. Marplan has shown markedly fewer of the side reactions of the hydrazines. Moreover, throughout the extensive clinical investigations, no liver damage has been reported. Marplan is an amine oxidase regulator, however, and like all of these agents, it is contraindicated in the presence of liver or kidney disease.

Consult complete literature and dosage instructions, available on request, before prescribing.

Bibliography: 1. Clinical reports on file, Roche Laboratories. 2. W. Hollander and R. W. Wilkins in J. H. Moyer, Ed., *Hypertension*, Philadelphia, W. B. Saunders Co., 1959, p. 399. 3. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 4. I. Kimbell, paper read at Co-operative Chemotherapy Studies in Psychiatry, 4th Annual Research Conference, Memphis, Tenn., May 20-22, 1959.

MARPLAN®—1-benzyl-2-(5-methyl-3-isoxazolylcarbonyl)hydrazine ROCHE®

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to lift depression

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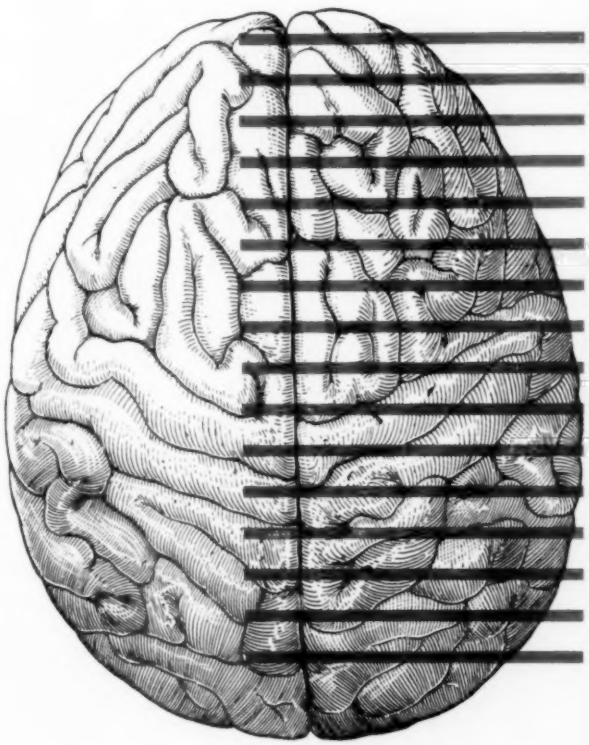
Marplan in rheumatoid arthritis: Marplan has also been found to be valuable adjunctive therapy in the management of rheumatoid arthritis and other chronic debilitating disorders with associated depressed psychomotor activity.



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mm.Hg*

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Added benefits: Lowered dosage requirements, fewer side effects • Improved renal blood flow • Relaxed cerebral vascular tone • Excellent diuresis in decompensated cases

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* Response of 56-year-old female patient noted in clinical report to CIBA.

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WITHOUT DIETARY RESTRICTIONS[1,2]

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capsules

In a recent report[1] on 44 patients, VASTRAN FORTÉ reduced plasma cholesterol levels to normal in 21 patients and lowered cholesterol levels by at least 40% in 14 more patients during a 30-week period. *There was no change in diet.*

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Each VASTRAN FORTÉ Capsule contains: nicotinic acid, 375.0 mg.; ascorbic acid, 50.0 mg.; riboflavin, 2.5 mg.; thiamine mononitrate, 5.0 mg.; pyridoxine hydrochloride, 0.5 mg.; calcium pantothenate, 2.5 mg.; cobalamin concentrate (vitamin B_{12} activity), 10.0 mcg. **Dosage:** Initial Dosage—2 capsules four times a day after meals for twelve weeks. Thereafter dosage should be adjusted according to response. Maintenance requirements may vary from 1 capsule q.i.d. to 4 capsules q.i.d. **Supply:** Bottles of 100.

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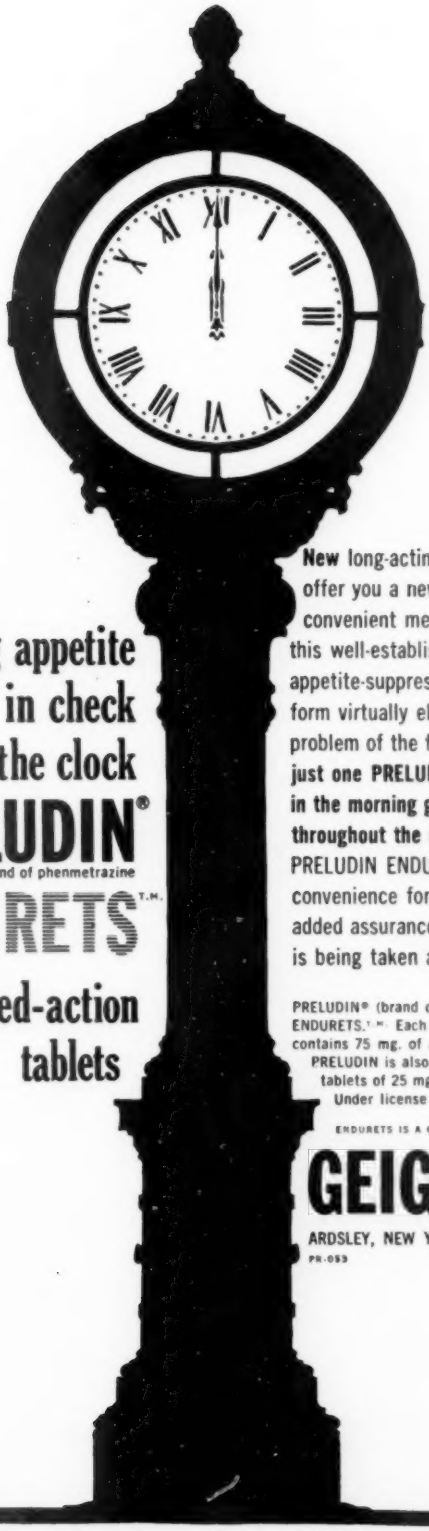
Bibliography: 1. Parsons, W. B., Jr., and Flinn, J. H.: A.M.A. Arch. Int. Med. *103*:783, 1959. 2. Parsons, W. B., Jr., and Flinn, J. H.: J.A.M.A. *165*:234 (Sept. 21) 1957. 3. O'Reilly, P. O.: Canad. M. A. J. *78*:402 (March 15) 1958. 4. Altschul, R., and Hoffer, A.: Arch. Biochem. *73*:420, 1958. 5. Achor, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, B. F.: Circulation *17*:497, 1958. 6. Altschul, R., and Hoffer, A.: Circulation *16*:499, 1957. 7. Hoffer, A., and Callbeck, M. J.: J. Ment. Sc. *103*:810, 1957. 8. Parsons, W. B., Jr., and Flinn, J. H.: Circulation *16*:499, 1957. 9. Achor, R. W. P.; Berge, K. G.; Barker, N. W., and McKenzie, B. F.: Circulation *16*:499, 1957. 10. O'Reilly, P. O.: Demay, M., and Kotlowski, K.: Arch. Int. Med. *100*:797, 1957. 11. deSoldati, L.; Stritzler, G., and Balassanian, S.: Prensa méd. argent. *44*:3286 (Nov. 8) 1957. 12. Parsons, W. B., Jr., *et al.*: Proc. Staff Meet. Mayo Clin. *31*:377 (June 27) 1956. 13. Altschul, R; Hoffer, A., and Stephen, J. D.: Arch. Biochem. *54*:588, 1955. 14. Seebrell, W H., and Harris, R. S.: The Vitamins; Chemistry, Physiology, Pathology, New York, Academic Press, 1954, vol. 2, p. 551. 15. Gregory, I.: J. Ment. Sc. *101*:85, 1955. 16. Sinclair, H. M.: Lancet *1*:381, 1956. 17. Page, I. H., *et al.*: J.A.M.A. *164*:2048 (Aug. 31) 1957. 18. Rosenfeld, L.: Am. J. Clin. Nutrition *5*:286, 1957.



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around the clock

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prolonged-action
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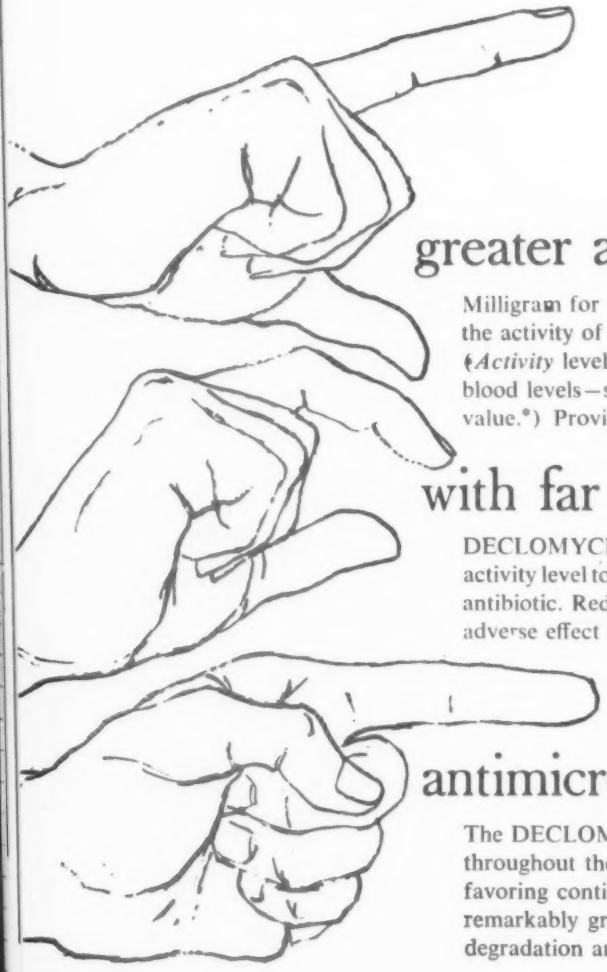

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DECLOMYCIN demonstrates the highest ratio of prolonged activity level to daily milligram intake of any known broad-spectrum antibiotic. Reduction of antibiotic intake reduces likelihood of adverse effect on intestinal mucosa or interaction with contents.

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The DECLOMYCIN high activity level is uniquely constant throughout therapy. Eliminates peak-and-valley fluctuation, favoring continuous suppression. Achieved through remarkably greater stability in body fluids, resistance to degradation and a low rate of renal clearance.

*Hirsch, H. A., and Finland, M.: *New England J. Med.* 260:1099 (May 28) 1959.

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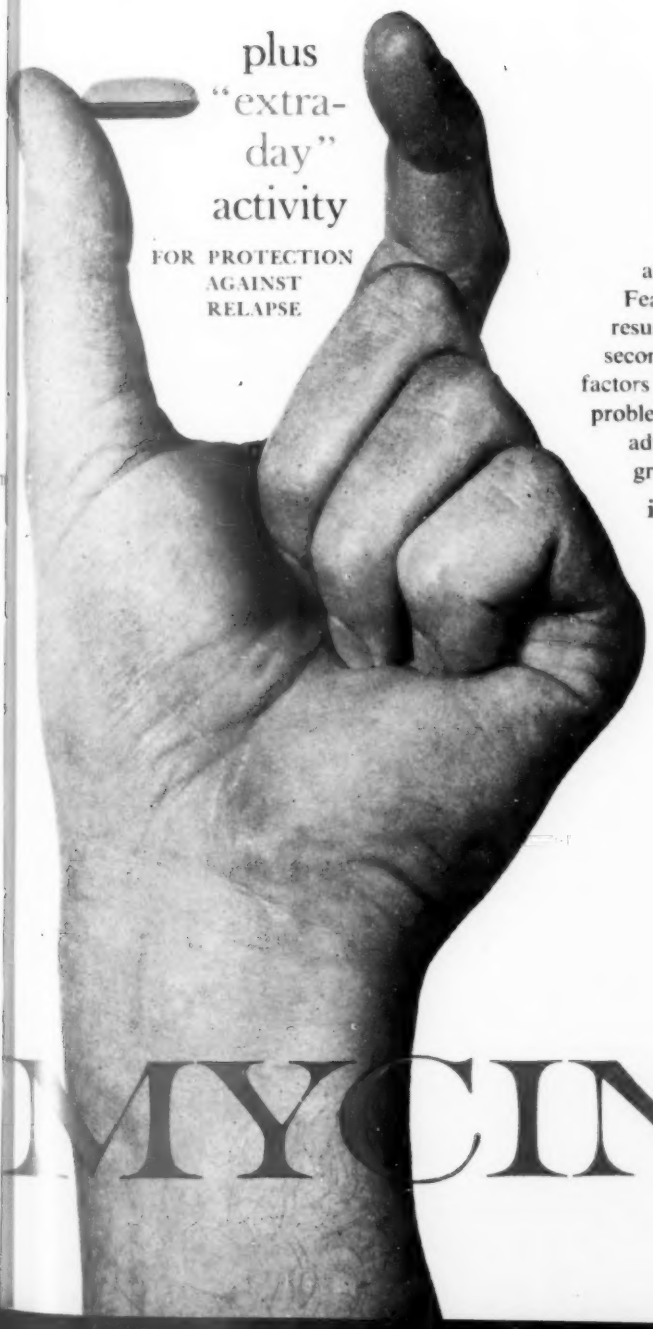

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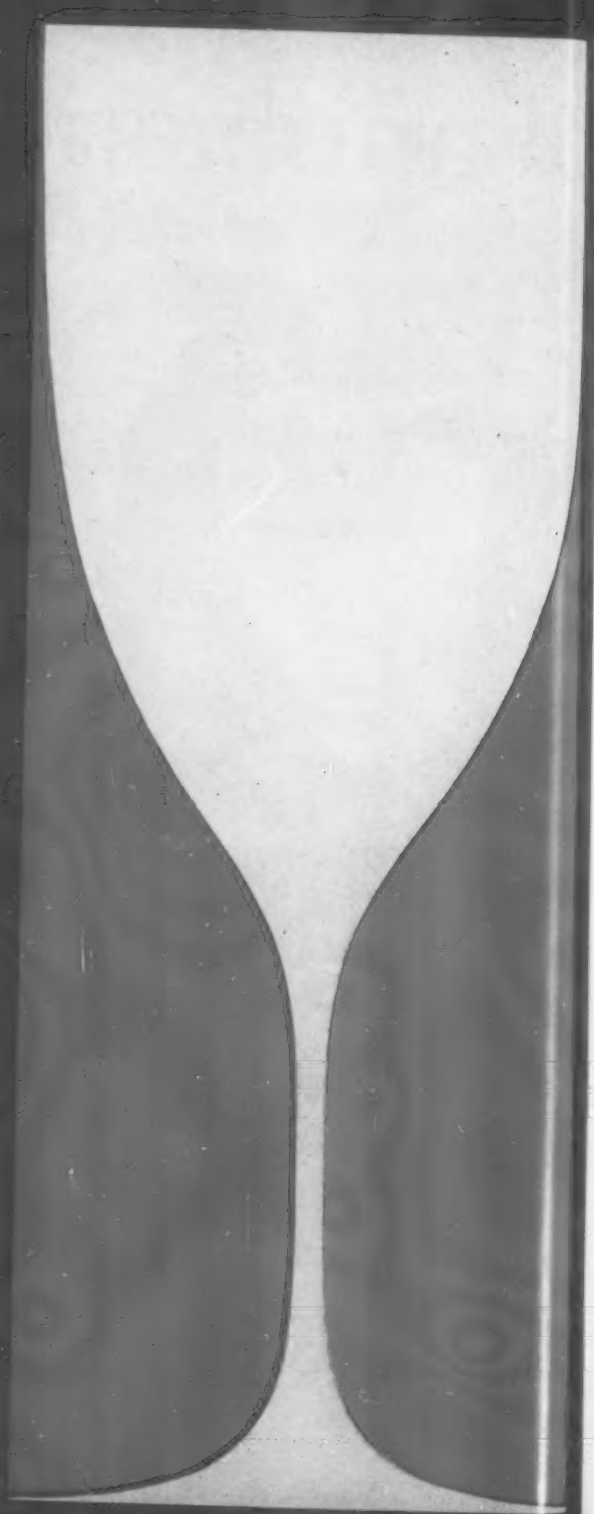

measured calories for adequate nutrition
with high satiety on 900 calories a day...
without appetite depressants

METRECAL*

DIETARY FOR WEIGHT CONTROL

no appetite depressants needed

Metrecal permits your patients to control their weight—effectively, comfortably, safely, by the application of sound nutritional principles *alone.*

adequate nutrition on 900 calories

Metrecal is a scientifically blended powder consisting of protein, carbohydrate and fat plus vitamins and minerals. One half-pound, the daily feeding, supplies 900 calories. It mixes readily with water to make a pleasant-tasting beverage.

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A gratifying feature is its high satiety value. Overweight patients placed on Metrecal alone comment on the absence of hunger, an improved sense of well-being and stepped-up motivation to lose weight.[1]

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flexibility in use

When more than 900 calories are permitted, the daily allotment (½ pound) of Metrecal may be increased—or it may be used with low-calorie foods.

special Metrecal weight-control guide

This instructive booklet, for distribution to your patients, will simplify giving instructions and help encourage patient cooperation. Ask your Mead Johnson representative for your supply.

(1) Antos, R. J., to be published. (2) Tullis, I. F, to be published.

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Note: Parents and patients should be informed that POVAN SUSPENSION will color the stools a bright red and that, if spilled, will stain.

Supplied: POVAN SUSPENSION is available as a pleasant-tasting, strawberry-flavored suspension containing the equivalent of 10 mg. pyrvinium base per cc., in 2-oz. bottles.

(1) Beck, J. W.; Saavedra, D.; Antell, G. J., & Tejeiro, B.: Am. J. Trop. Med. 8:349, 1959.

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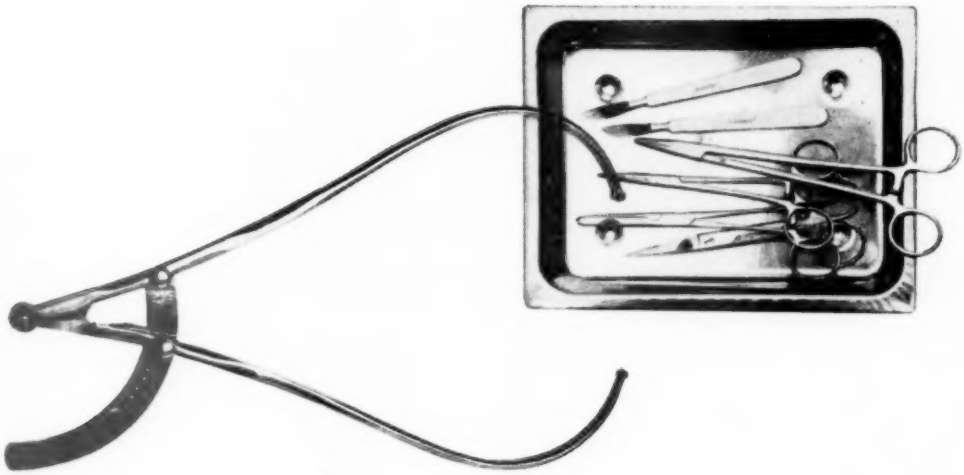

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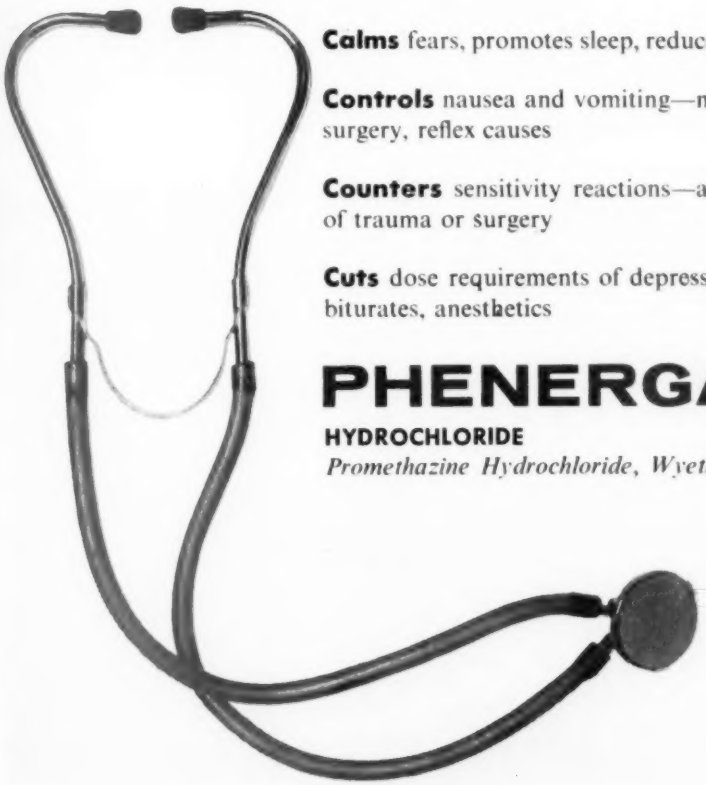
MEDICINE
SURGERY
OBSTETRICS



Calms fears, promotes sleep, reduces postoperative excitement

Controls nausea and vomiting—motion sickness, pregnancy, surgery, reflex causes

Counters sensitivity reactions—allergy, drugs, tissue edema of trauma or surgery

Cuts dose requirements of depressant agents—narcotics, barbiturates, anesthetics

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Promethazine Hydrochloride, Wyeth

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SUPPOSITORIES
INJECTION

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Before Esidrix:
Weight 176 lbs.

27 pounds lost in 19 days; ascites and

RECORD OF TREATMENT (At a leading New York City hospital. Photos used with permission of the patient.)

Date	3/3	3/4	3/5	3/6	3/7	3/8	3/9	3/10	3/11	3/12	3/13	3/14	3/15	3/16	3/17	3/18	3/19	3/20	3/21	3/22	3/23
Weight (pounds)	178	176	170	169	167	159	158	158	157	153	155	155	156	154	153	154	153	—	—	151	149
Rx	M*	Esidrix 50 mg. b.i.d.																			

*Mercurial diuretic

Esidrix T.M.

(hydrochlorothiazide CIBA)

pre-eminently effective whenever diuresis is desired

Indicated in: congestive heart failure . . . nephrosis and nephritis . . . toxemia of pregnancy . . . premenstrual edema . . . edema of pregnancy . . . steroid-induced edema . . . edema of obesity

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CIBA
SUMMIT, N. J.

After 19 days on Esidrix:
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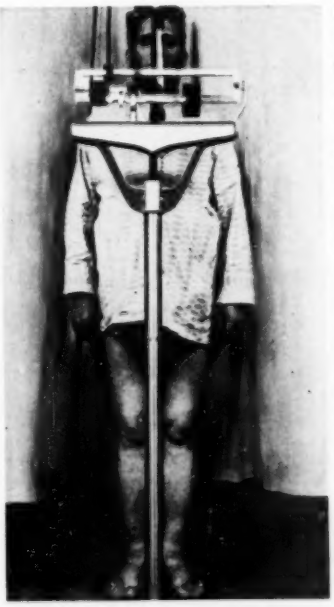
pedal edema reduced with Esidrix

H. K., 44 years old, was admitted to the hospital on 3/3/59 with complaints of *swollen abdomen, swelling of both legs and exertional dyspnea.* These symptoms had been intensifying over a three-week period. The patient's history included heavy drinking since the age of 18, and one prior admission to the hospital in 1954 with ascites and pedal edema. Diagnosis, at that time, was Laennec's cirrhosis, and the patient responded well to a regimen of diuretics, salt restriction and multivitamins. There was no recurrence up to that leading to his current admission.



Clinical findings worthy of note: Eyes — conjunctivae and sclerae slightly icteric. Chest—diaphragm elevated. Abdomen — girth enlarged, definite fluid wave. Liver palpated 4 fingerbreadths below the costal margin; no other palpable viscera. Extremities—pedal edema (4+).

The patient is well developed and not in acute distress. Blood pressure, 140/80 mm. Hg; pulse, 112/min.; respiration, 20/min. Impression: Laennec's cirrhosis—decompensated.

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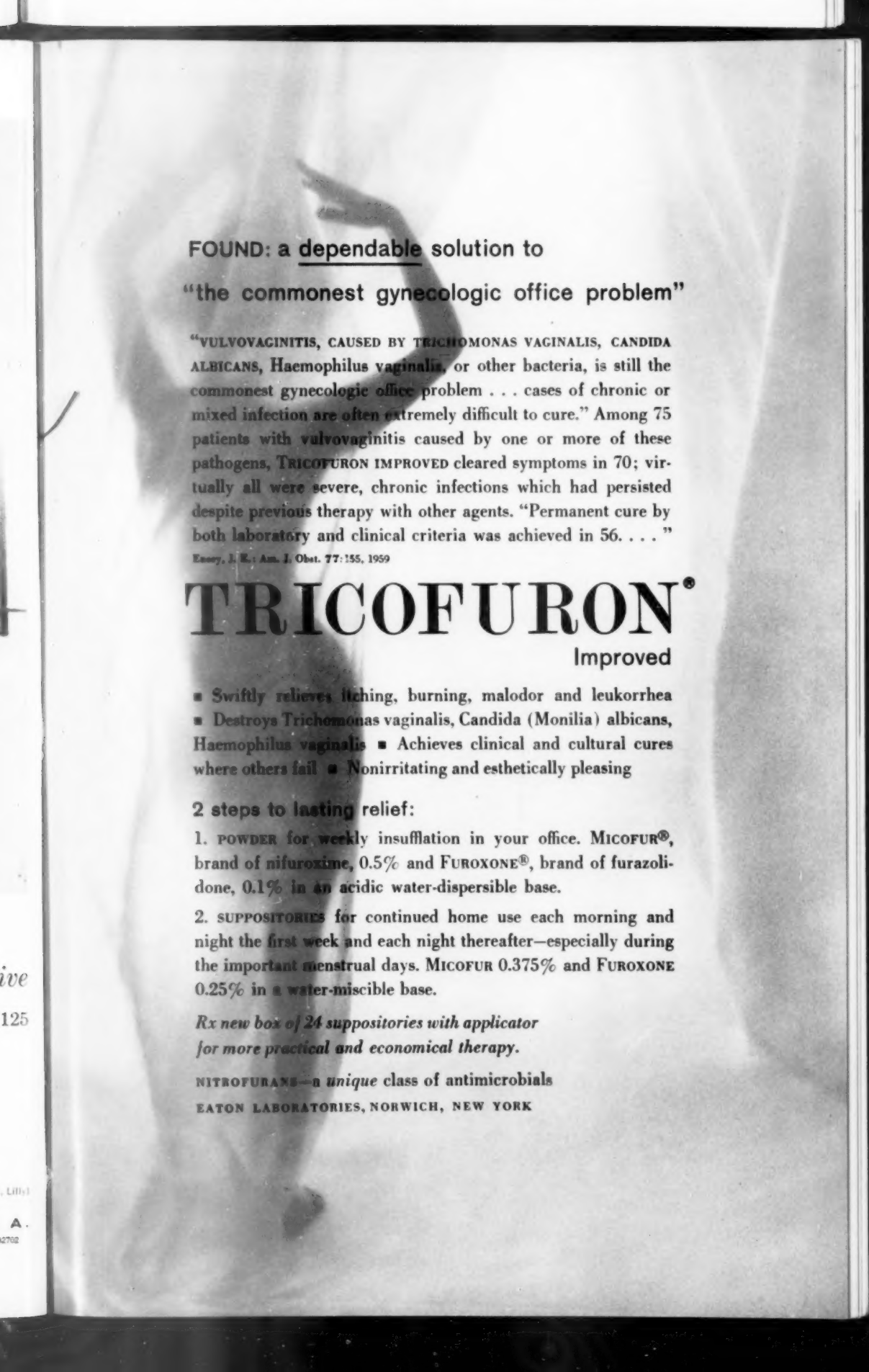

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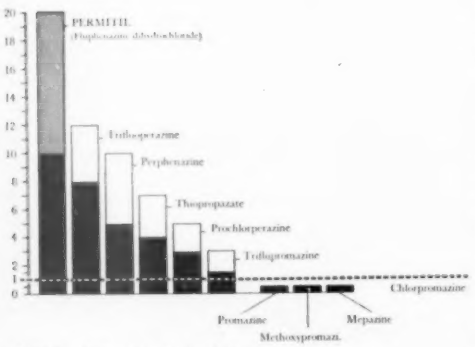

Adapted from Ayd, F. J., Jr.[3]

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References: 1. Freyhan, F. A.: Psychopharmacology Frontiers, Boston, Little, Brown and Co., 1959, p. 7. 2. Ayd, F. J., Jr.: Fluphenazine: its spectrum of therapeutic application and clinical results in psychiatric patients, Current Therapeutic Research, 1:41 (Oct. 15) 1959. 3. Ayd, F. J., Jr.: The current status of major tranquilizers, in press.

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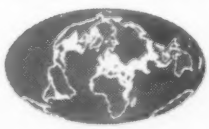

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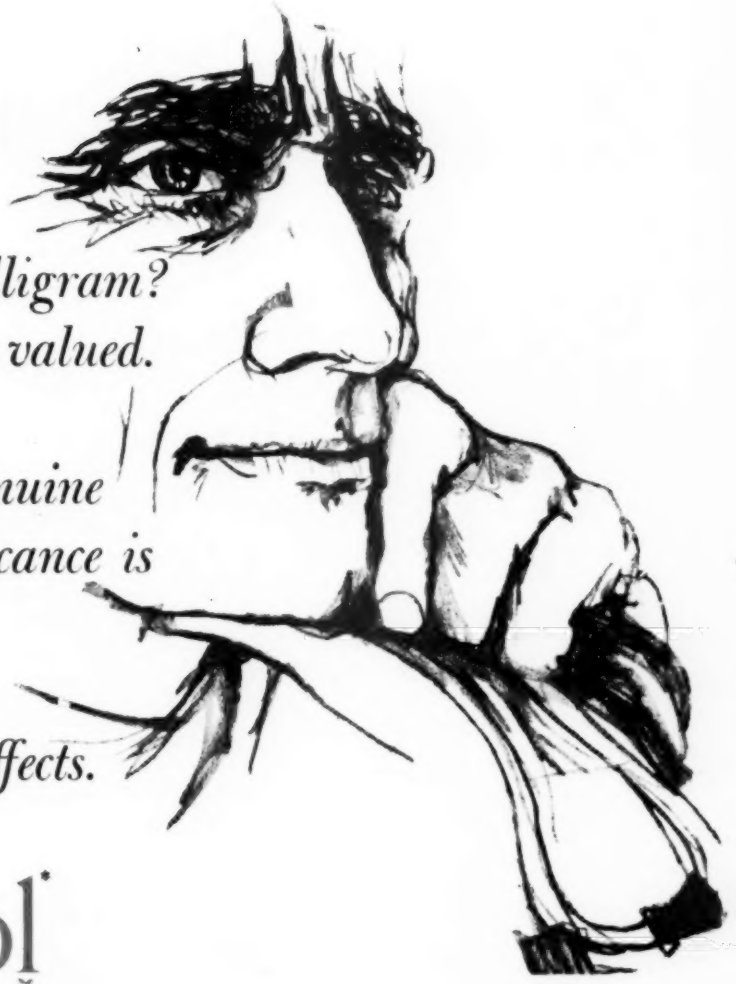

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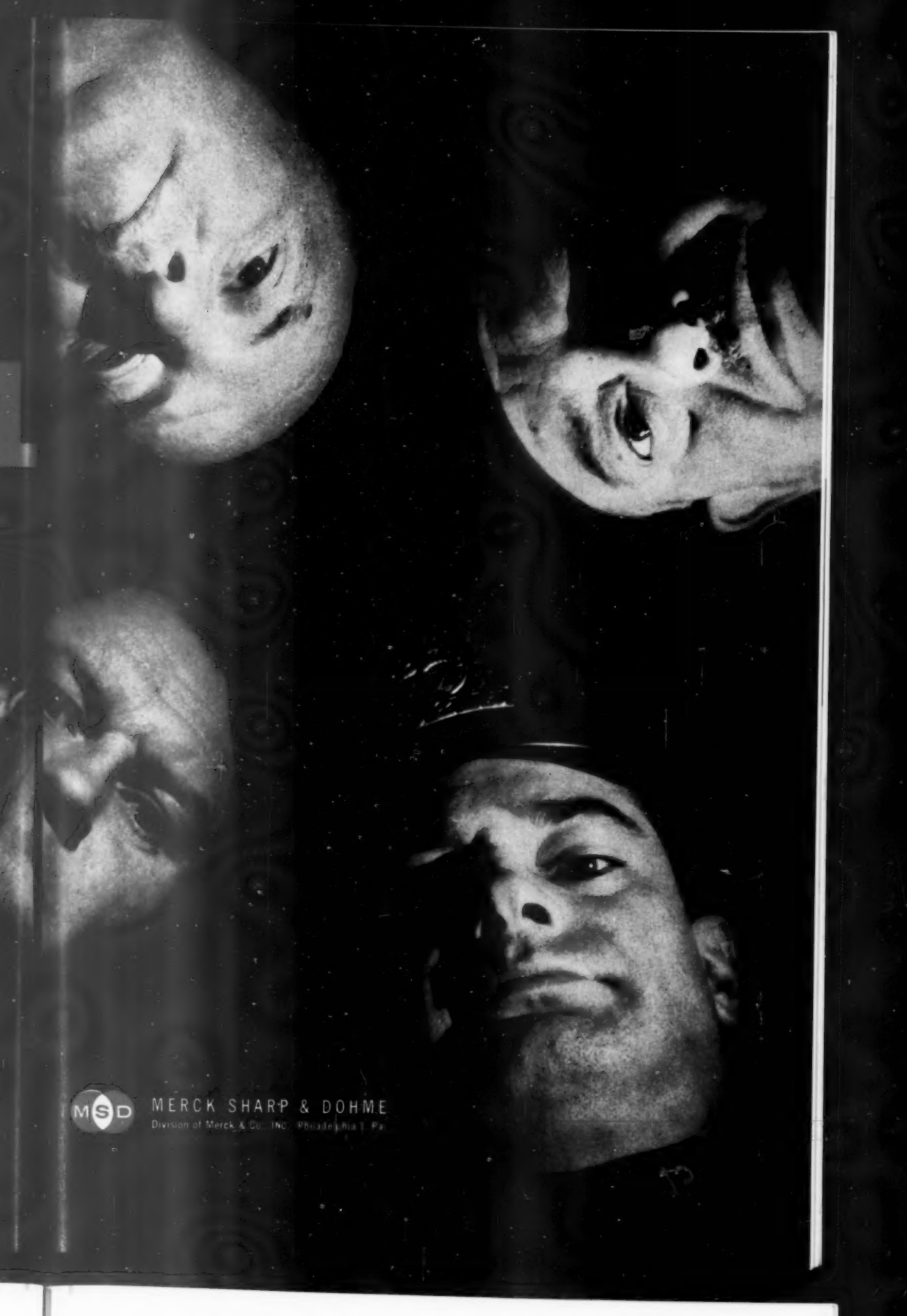
1. Selzer, A. and Rytand, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.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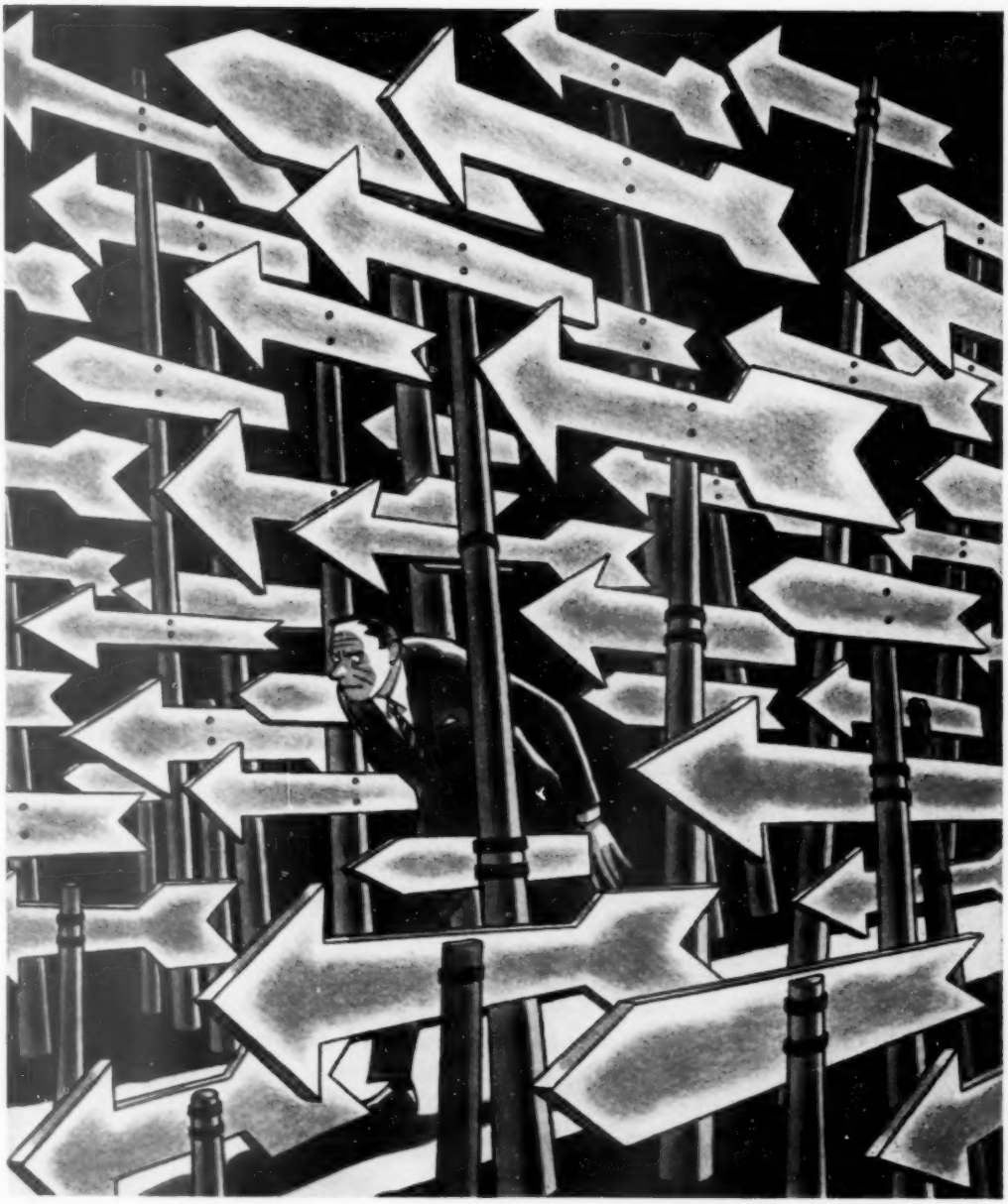

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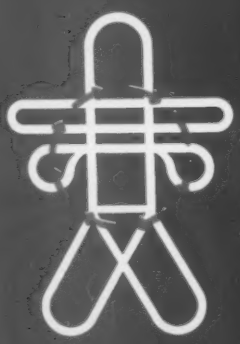

1. Moser, K. M.: J.A.M.A. *167*:1695 (Aug. 2) 1958.
2. Clifton, E. E.: J. Am. Geriatrics Soc. *6*:118, 1958.
3. Sussman, B. J., and Fitch, T. S. P.: J.A.M.A. *167*:1705 (Aug. 2) 1958.
4. Singher, H. O., and Chapple, R. V.: Clin. Med. *6*:439 (March) 1959.

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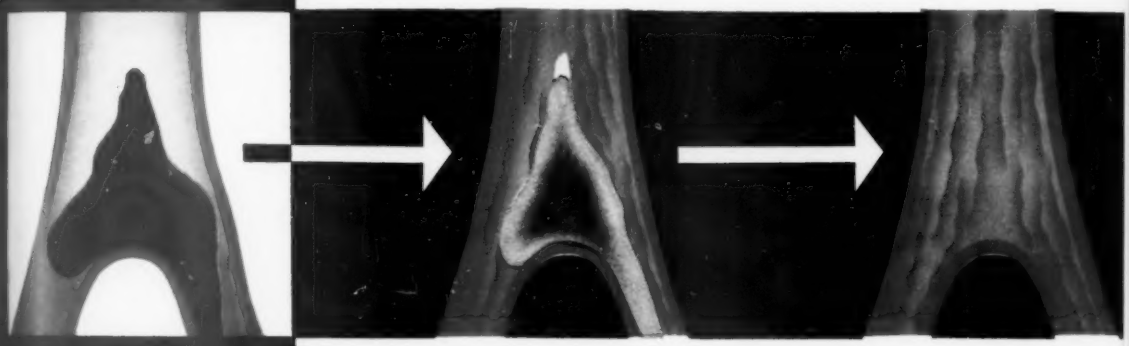

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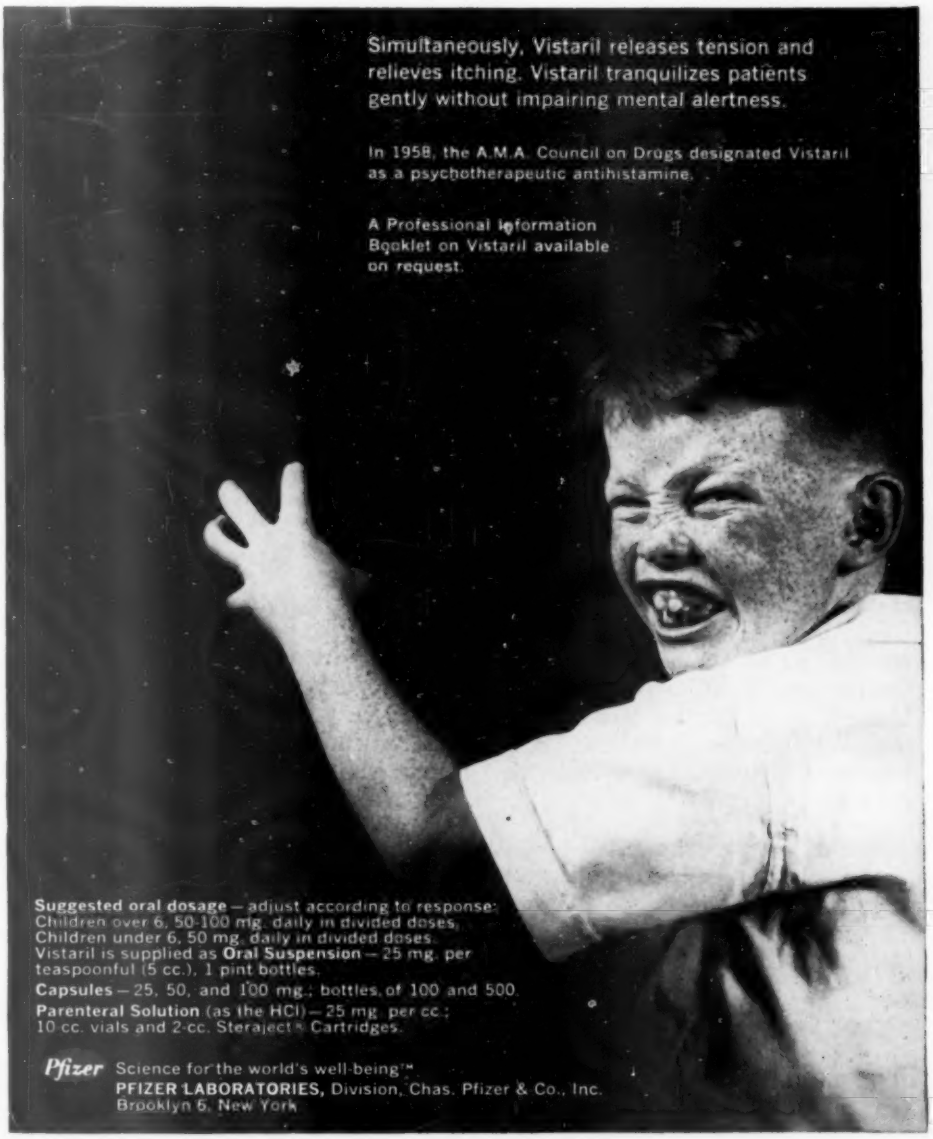
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1. Whitelaw, J.W.: Hypoparathyroidism in Children. *Bull. Vancouver Med. Assn.*, 30:116, Dec., 1953.
2. Sandock, Isadore: Tetany and Ovarian Function. *J.A.M.A.*, 160:659, Feb. 25, 1956.
3. Grollman, Arthur: Essentials of Endocrinology. Philadelphia, J. B. Lippincott Co., 2nd ed., 1947, p. 269.

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